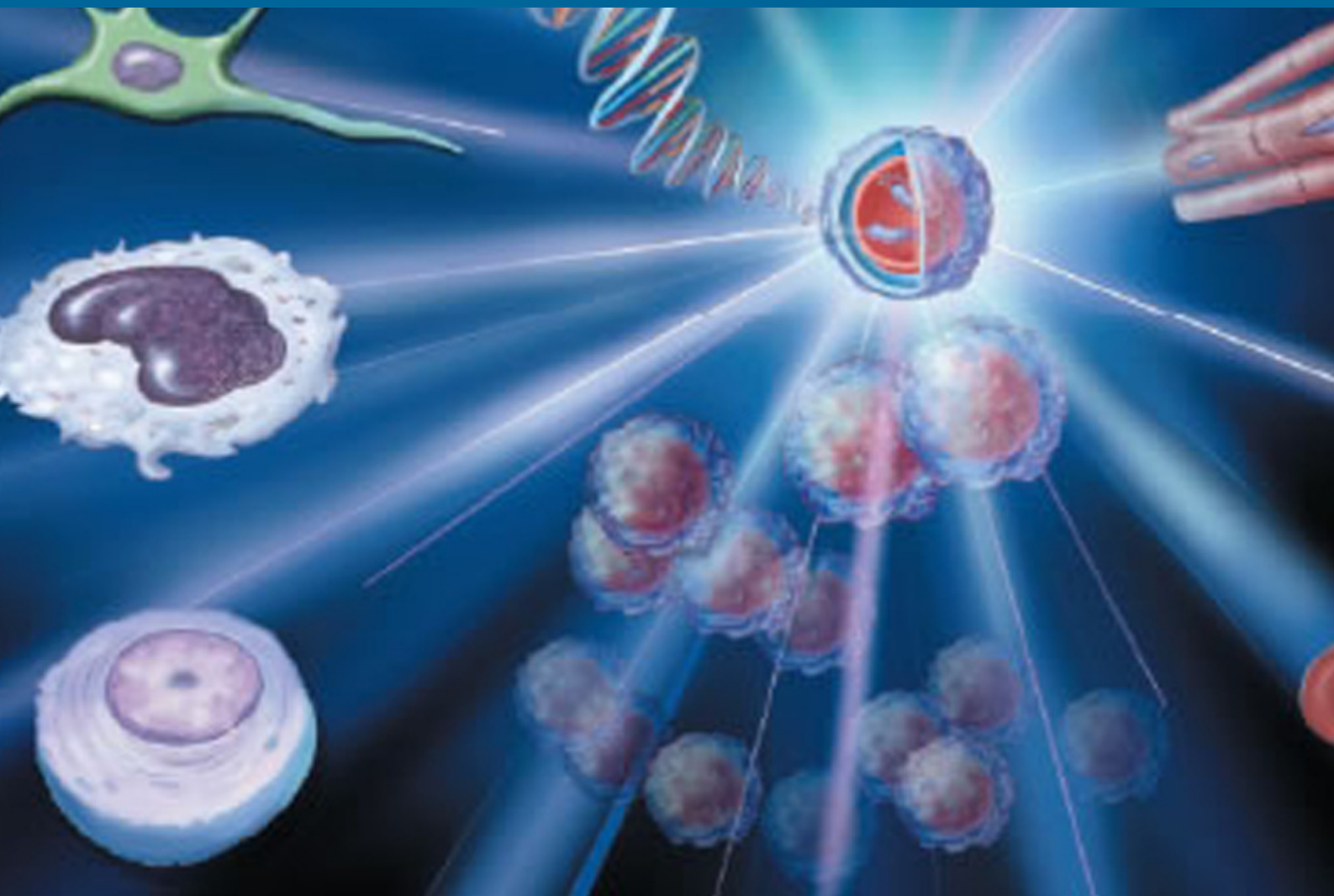


IBSscientific

A Peer Reviewed Open Access Magazine

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Stem Cells
[Google Images]

PRIMER: Stem Cells

An Overview of the Current and Future Trends in Stem Cells Research

Also Inside:

Interview with Dr Steven Pollard
The Story of COX-2 Inhibitors
Networks On-Chip
Embryonics Systems

IBScientific
An Open Access Scientific Magazine

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On The Cover

Stem Cells are the
most important dis-
covery since the
Watson/Crick helix.

The Journey So Far...

The editorial board of IBScientific is very pleased to present the second issue of the magazine, which is the result of a greater effort and determination all the participants have shown.

The first issue of IBScientific was launched last term and was enthusiastically received. We are thrilled with the response and glad that you, the readers, agree with us that there is a real niche for what we are trying to achieve. The transition from the first to the second issue has marked an exciting period of intense evolution for our magazine. One of our goals from the previous issue was to broaden the scope of our articles and to get the standard of the writing one step up, which I hope you will agree we have remarkably improved upon for this issue.

We hope that you have had a chance to visit our website, launched in conjunction with the first issue, and join our scientific forum to share your views and ideas with the other members. Through our website, you can access all the content of the magazine which is available in different formats to suit your needs. The website is updated every week with up-to-date scientific news from several disciplines. For more information, visit www.ibscientific.net.

We hope that, by giving Algerian scientists a chance to express themselves, we have managed to entertain non-scientists and scientists alike, and provided for everyone, in the United Kingdom and outside, the opportunity to get together as part of a larger scientific community.

We have no intention of restraining our ambitions for the coming issues, and have plenty of ideas which we aim to achieve in order to establish ourselves firmly as a scientific magazine. During the last term, we have made some changes to the team organisation. We have now adopted a deadline system for receiving, reviewing and proof-reading articles. We have also split into three work groups; physical sciences, life sciences and social sciences. For each group, a chief reviewer, appointed by the editor-in-chief, is responsible for assigning reviewing tasks to our reviewers, which is done in complete anonymity.

Currently, we are working to improve our website for better communication and ease of navigation and trying to broaden

IBScientific

the scope of our articles even more to appeal to a larger group of budding science journalists out there. So if you are interested in contributing to IBScientific, or have any ideas that you would like to share, then please get in touch.

We strongly believe communication is crucial to scientific research. If you are driven by enthusiasm for your field, as we are, you will want to tell people about it. IBScientific is your platform; I hope you will take advantage of it. If you just want to get on with your research, then send us your news and give others the opportunity to read about it. We have worked hard to put together a magazine for you. If you are passionate about communicating science and think we can do better, we would love to hear from you.

Finally, I would like to say many thanks for all the positive feedback you have sent in, as well as technical corrections and comments - we are still striving for perfection!

I very much hope you enjoy our second issue. ■

Sofiane NACI
IBScientific Editor

IBScientific

<http://www.ibscientific.net>

IBScientific is published termly by a group of Algerian students in the United Kingdom. It is open to all contributions from all disciplines. The editorial team is not responsible for the opinions expressed in IBScientific.

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Astronomy

The Eclipse That Uncovered Ramadan's Moon

Prof. Mimouni, president of the scientific committee of



Shaara society for Astronomy, has said that the moon due to be seen on the eve of the 2nd October 2005 "is a wrong forecast for Shaaban's moon because of the Annular Solar eclipse¹ on the 3rd October 2005; and based on that, Ramadhan's moon is impossible to have formed and seen by that time"

The professor from the Physics Institute (Mentouri University, Constantine, Algeria) has explained, based on astronomical calculations, that the first day of Ramadhan will be the 5th October and not before because the moons cycle will not have completed, hence, Shaaban will have 30 days this year.

Although the path of the annular solar eclipse begins in the North Atlantic, Spain and Portugal, it will also cross the Algerian capital Algiers within the shadow trajectory and will experience an annularity of 3min 51sec. This event is rare for a specific location and the last eclipse of this kind in Algeria was back in 30 May 1984, and it is predicted to

happen again in 01 June 2030 (there will be one partial predicted on 29 March 2006) which makes it the most important astronomical phenomenon this year.

Source: Elkhbar 13/09/2005. A.B.

Computing



ARM Partner Meeting Cambridge 17-19 Aug 2005

The APM (ARM Partner Meeting) is an event held by ARM and its growing partnership to demonstrate hardware and software solutions offered by ARM. ARM is the industry's leading IP (Intellectual Property) provider of 16/32-bit embedded RISC (Reduced Instruction Set Computer) microprocessor solutions. ARM 16/32-bit RISC microprocessors, data engines, peripherals, software and tools, combined with the company's broad Partner community, provide a total system solution that offers a fast, reliable path to market for leading electronics companies. ARM partners community includes a large number of companies from application developers (e.g. Accelerated Technology, Microsoft and Green Hills); silicon manufactures (e.g. Texas Instruments, Intel, and Philips) and tools vendors (e.g. Cadence, Synopsys and Mentor Graphics).

The main new technologies shown in the event were MPCore and OptimoDE. The MPCore represents the ARM multiprocessor architecture; it effectively contains many

CPUs in one chip. The demonstrated demo showed the MPCore with four CPUs running Linux OS. The CPUs can be switched on and off according to the required work load; this improves performance and reduces power consumption significantly.

The OptimoDE is an extremely configurable data engine architecture, targeted at intensive non-stop data processing (e.g. mp3 decoding). OptimoDE offer an unrivalled combination of advanced logic, robust functionality, energy efficiency and efficient silicon utilisation.

The APM also demonstrated the latest technologies provided by ARM. Examples of hardware solutions includes MBX (3D graphics engine with OpenGL-ES support), Jazalle (Java bytecode acceleration hardware), and the new AMBA 3 (AXI) bus architecture (on-chip bus). The software side includes the IEM (Intelligent Energy Manager) and Swerve (Java 3D library implementation).

Source: ARM Ltd, Cambridge. A.M.

Lab-On-Chip - What is the Next Level Down?

Dr. Chris Backhouse, a researcher from the University of Alberta's Department of Electrical and Computing Science and co-leader of Alberta Cancer Diagnostic Consortium (ACDC), is inspired by the miniaturisation of electronic chips and wants to achieve the same innovation with Lab-On-Chip. The scale of integration of electronic chip has undergone a rapid evolution according to Moore's Law from thousands of transistors to billions now in a single chip. It was only few years back we heard about the Systems-On-Chip (SoC) and then Networks-on-Chip (NoC) (1) and now Lab-On-Chip (LoC). This little piece of

glass and polymer plate with tiny tracing inside will replace the complex process for testing for cancer. Usually, these tests are expensive and carried out in clinics which suffer from a longer time to provide patients with rapid treatment. This innovation will cut down the cost and time and will enable doctors to tailor the medication specifically to each patient.

"Testing on fast, sensitive, automated microfluidic devices can warn of potential adverse drug effects, monitor vaccination efficiency, detect disease-related genetic abnormalities, all for the design of personalised medicine," Dr. Linda Pilarski, a cancer researcher at the University of Alberta who co-leads the ACDC, said.

Pilarski says test have already begun using LoC and they are now in a phase to start clinical trials with a genetic test involving childhood lymphocytic leukemia. To this present time, the conventional testing means, in Canada, could not be carried out because of the high cost and complexity. Another test adapted for on-chip testing involves looking for chromosomal abnormalities in molecular myeloma and follicular lymphoma. A third test consisted of detecting high viral loads in urine samples.

Pilarski, explaining the revolution that could brought by this technology, said: "Imagine a Canada where complex medical test results are avail-

¹ An annular eclipse differs from a total eclipse in that the Moon appears too small to completely cover the Sun. As a result, the Moon is surrounded by an intensely brilliant ring or annulus formed by the uneclipsed outer perimeter of the Sun's disk. The solar corona is not visible during annular eclipses. Furthermore, a solar filter or projection is needed to observe all phases of an annular eclipse.

(1) Mammeri, N. (2005). IBScientific. 2 (1), 33-34.

able almost instantly, where aging Canadians can perform home-based testing with almost instantaneous transmission to a doctor's office, where emerging or relapsing cancer can be rapidly detected in local healthcare centres, where high quality healthcare is easily available on the farm, in the mountains, on the high Arctic tundra, or even in outer space. ACDC is creating robust, adaptable and transformative technologies for fast, highly accurate at the point of care, in the field and on the spot."

Source: *PhysOrg.com*. 16/08/2005. A.B.

Physics

Marvel of Modern Science

Eric Cornell¹ et. al at the University of Colorado in Boulder and JILA, have been able to measure the so called Casimir-Polder (1) force with very high precision using Bose-Einstein condensates (BECs²) of atoms. This is the first direct application of BEC in measurements which marks the beginning of their evolution from research focus to laboratory tools.

Although the average electric field is zero, the quantum theory tells us that there are very small fields everywhere changing in magnitude and direction

with time. Casimir and Polder derived mathematically in 1948 that these fluctuations increase when they are in the vicinity of a surface, but the net sum remains null. This means that if an atom happens to be floating in the surrounding region, it will be attracted towards the surface as a magnet pulling a paper clip. However, it was until 1993 where Sukenik et al (2) have finally measured this force with great confidence.

The researchers at Colorado University created a few micron thick disk shaped cloud of atoms in BEC from rubidium and set it to oscillate vertically few microns below a silica plate using what is known as a magnetic trap. Then, they measured the frequency of perturbation in a range of different distances from 6 - 10 microns. The force could thus be determined from the frequency measurements. The breakthrough has been achieved as other research teams were not able to measure the Casimir-Polder force beyond 2 microns from the plate and the Colorado team also detected forces hundreds of times weaker at closer distance which are in agreement with the theoretical results (3). Yet, the team is hopeful to detect the modification due to thermal radiation.

Steve Lamoreaux of Los Alamos National Lab in New Mexico, who first cleanly measured the Casimir force, calls the experiment a "marvel of modern science."

Source: *Physical Review Focus*. 08/09/2005. A.B.

The League of Truly Unique Physicists... and Biologists

IN recent decades and with the increase in the number of scientists competing for funding, it is a necessity to have criteria for awarding such and other

privileges. Institute of scientific information have gone a long way to achieving that by creating impact factors for journals for each field and citation reports for scientists. In the latter the weight of the scientist is calculated by the number of citations of the papers they authored. This has the problem of inflating the rating of scientists if they co-authored lots of high citation papers that they merely have their name on. In order to eliminate such problem, Jorge Hirsh of the University of California has proposed a new and improved variable: the h-index. A scientist with an h-index of 10 would have published 10 papers that were cited at least 10 times each. In order to prove this new method feasibility, he looked at h-indexes of some physicists he thinks highly off, and are respected as the best in their perspective field and found very good correlation. The highest h value in physics goes to Edward Witten with h=110, a string theorist from the institute of advanced study in Princeton. Other highly ranked physicists include: Marvin Cohen, a condensed matter theorist at the University of California at Berkeley; Philip Anderson, a condensed matter theorist at Princeton University; Steven Weinberg, a particle theorist at the University of Texas at Austin; and Michael Fisher, a mathematical physicist at the University of Maryland.

In life sciences h values are considerably much higher concluded Hirsch (h=49). The highest being 191 for Solomon Snyder, a neuropharmacologist from Johns Hopkins University. Other high h ranking biologists includes David Baltimore, a cell biologist from California Institute of Technology; Robert Gallo, a virologist from University of Maryland School of Medicine; Bert Vogelstein, a cell biologist from Howard Hughes Medical Institute; and Salvador

This issue's news were collected by:

AE: Ablekader Essafi

AK: Abderrahmane Kaidi

AB: Abdeldjalil Bennecher

AM: Ahmed Maache

Moncada, a pharmacologist at UCL.

Hirsh went a step further proposing a link between promotions and h values. A researcher should be promoted to associate professor at around an h value of 12, and to a full professor at around 18. He also looked at earlier scientists and suggested that a successful scientist is the one who has an h value of 20 in twenty years, outstanding at h=40, truly unique at h=60 if achieved in twenty years.

It is also important to note that the h value differs from one sub-speciality to the next in the same discipline, and that every body should take care while comparing between scientists from different fields.

Source: Hirsch, JE, *Physics*. 2005. http://arxiv.org/PS_cache/physics/pdf/0508/0508025.pdf. A.E.

Cancer Medicine

Aspirin... Again!!

FOR 20 years, researchers at Massachusetts General Hospital have been studying more than 80,000 women to see if aspirin could reduce the risk of colon cancer.

The findings, published in the *Journal of the American Medical Association*, are impressive (Andrew et al). Women who took more than 14 tablets a week for ten years did reduce their risk of colon cancer by half. But there's a downside. Researchers also found that all those tablets caused a greater risk of bleeding in the stomach and intestines.

The bottom line in the JAMA report is that regular screen-

¹ a cloud of ultra cold atoms coalesce into the same quantum mechanical state.

² Nobel Prize laureate in Physics 2001 for his work on BEC

(1) Casimir, H.B.G., and Polder, D. (1948). The Influence of Retardation on the London-van der Waals Forces. *Phys. Rev.* 73, 360.

(2) Sukenik, C.I., et al. (1993). Measurement of the Casimir-Polder Force. *Phys. Rev. Lett.* 70, 460.

(3) Antezza, M., Pitaevskii, L.P., and Stringari, S. (2004). Effect of the Casimir-Polder Force on the Collective Oscillations of a Trapped Bose-Einstein Condensate. *Phys. Rev. A* 70, 053619.

ings are still the best way to protect yourself against colon cancer.

Source: Andrew T, et al. (2005). Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer. *JAMA*. 294, 914-923. A.K.

Neuroscience

Even Monkeys Like to Have a Punt, and Will Persist in Hope of the Jackpot

Most casino owners are rich. Most gamblers are not. I have thus deduced that gambling is no way to happiness. Try telling that to macaque monkeys. They get such a thrill out of betting that, like people, they are willing to incur huge losses in the hope of an eventual win.

Michael Platt and Allison McCoy, from Duke University Medical Centre in North Carolina, set up two target lights for male rhesus macaques (Allison N McCoy and Michael L Platt, 2005). The reward for looking at one light was a cup of fruit juice. The reward for looking at the other light was also juice but the amount was unpredictable - sometimes there was more, sometimes less. The monkeys always preferred to take a punt on the unpredictable one, even though when averaged out the juice output for both targets was the same.

The researchers wondered if the preference might be due to the monotony of the procedure, so they made the target lights turn a different colour for each experiment. The monkeys still preferred to gamble. And, fascinatingly, even when the "gambling" light delivered a series of miserly juice portions, the monkeys hung on in there, perhaps waiting for a supersize juice. The unpredictability, Dr Platt theorises,

seemed more satisfying than the juice.

"It seemed very, very similar to the experience of people who are compulsive gamblers," says Dr Platt, who published the findings in *Nature Neuroscience*. "While it's always dangerous to anthropomorphise, it seemed as if these monkeys got a high out of getting a big reward that obliterated any memory of all the losses that they would experience following that big reward."

The gambling behaviour was mirrored by neuronal activity in the brain region associated with the processing of rewards. Similar studies in people may tell us why compulsive gam-

blers cling on to the mistaken belief that they are destined to win.

Source: McCoy, A.N., and Platt, M.L. (2005). Risk-sensitive neurons in macaque posterior cingulate cortex. *Nature Neuroscience*. 8, 1220-1227. A.K.

Engineering

Fly Softly, They Can Hear!

Dr. Reynolds, a representative of a unique research project - the Cambridge-MIT Institute's Silent Aircraft Initiative - has given a lecture in Trinity College Dublin (part of the festival of science) talking about the future of civil aviation. He presented a model of an air-

craft and played a short film showing the design of this air vehicle. The aim of this initiative is to invent a new way for quiet civil aircraft that its noise only extends to the airport circumference.

In the next 20 years air travel demand is forecast to double, and aircraft noise has become an important issue that needs to be tackled. Dr. Reynolds discussed the work the combined team is doing on three major noise sources from aircraft: the engines, the undercarriage, and the airframe - the physical structure of the plane, and rounds it all up by demonstrating what the Silent Aircraft could sound like!

For those who missed Dr. Reynolds' lecture in Dublin, you can watch it here: <http://www.cusp.org.uk/festival/>

Source: The Engineer Online. 15/09/2005. A.B.

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Where is Biology Going?

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IN recent years several debates have been ravaging about biological technologies, such as genetically modified organisms and Stem Cell sciences. In both cases, the scientists were accused of playing the hand of God and were producing unnatural entities and introducing them into our lives. From another point of view these two technologies are none other than the solution for some human basic problems: Starvation and Disease. The hopes built on these technologies have been fuelled significantly by misconceptions from the mass media. The public started taking sides while this field is in its infancy.

In this issue, Fella Essafi, ISCR, Edinburgh (1) has tried to clarify some misconceptions about stem cells. It not only highlighted their importance and state of affaire in this exciting field of research, but also gave a fresh look at the field terms of achievements and prospects. She has been able to introduce the field of stem cell biology with its ups and down. In frank and objective look, we can see the limitation experienced by this field at present and the possibilities that it might be able to offer.

The article was written as a reference for any one interested in stem cell research or debates. It started with definition and categorisation of stem cells, followed by a comparison between the different stem cells. This will allow the reader a grasp of basic stem cell biology, and prepare them for the applications cited and their effectiveness. In this latter section, the author clarifies the possibilities of some technologies and the timescale needed for their implementation.

To conclude, Essafi reminds us that this field is still in its infancy, and that there remain more questions to be asked than the few we have already answered.

The author also highlights new finding in ISCR that has opened a new way for stem cell biology. She has interviewed the author of the new study and discussed the importance of this discovery (2). All in all, the author presents a critical primer for stem cells, and cutting edge discoveries in one stroke. ■

(1) Essafi, F. (2005). *IBScientific*. 1 (2), 16-21.
(2) Interview. (2005). *IBScientific*. 1 (2), 21-22.

Another Martyr in The Name of Safety...

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IN the history of medicine drugs have been used and validated, and some have been withdrawn due to their side effects. Usually, these drugs are new and were never tried before and hence their side effects are not well documented. The late Vioxx/Celebrex fiasco can serve always as the best example approached by a paper in this issue of *IBScientific* (1).

There is, of course, the other side of the coin. There are certain drugs that are used but their efficiency is quite debatable. In this issue of *IBScientific*, Rabia Bourkiza, The University of Leeds attempted to clarify the role of corticosteroids in traumatic head injury (2).

Traumatic head injury is very common after accidents and claim lots of lives worldwide. Because of the injury to the cranial region, the patients are rushed for treatment to stop the bleeding, especially internal haemorrhage. Then a recovery period is followed if the situation is stabilised. In this period some drugs are used to help repair and regenerate some of the damaged brain tissue. Some of these drugs include steroids. The latter have been used extensively since the 1960s, and their use has debated ever since.

The literature on the above subject is scarce and spans for decades. It is also fragmented and contradictory, between

supporting the use of steroids and complete uselessness of the drugs as a therapeutic window. In this article, the author examines both sides of the argument and shows the limitations incurred in most studies. She has also been able to conclude the need for much larger clinical trials. While writing the article, a report was published showing the largest trial ever conducted for the use of steroids in TBI. More than 10,000 patients from 50 countries took part in the study. This study was successful in reducing the trust in corticosteroids use in head injury patients, but fails to establish a link between the mortality observed and the use of the drugs.

It is worth mentioning that this kind of study has the statistical credibility, but still suffers from the same drawback highlighted by the author for the earlier trials. The steroids were chosen as a therapy because of their effectiveness in some cases, and not because they eliminate or reverse the causes. More rational drug discovery is needed to tackle this problem.

That is not the end of the story; a lack of good biological systems and the speed of deterioration of patients do not give adequate opportunity for the study of the pathophysiology of the injuries. This case highlights not only the difficulty of medical research and the very stressful position of medical professions, but the never ending need for new therapies, and newer still... ■

(1) Mehellou, Y. (2005). *IBScientific*. 1 (2), 14-15.
(2) Bourkiza, R. (2005). *IBScientific*. 1 (2), 24-26.

COX-2 Selective Inhibitors... Is It The End of The Story?

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THE willow tree has for a long time been the pharmacy of choice that provided healing for headache, pain and fever. With no surprise the willow-tree even inspired the production of Aspirin®, by Bayer in 1899. But that was not the end of the story; John Vane (1927-2004) was awarded the Nobel Prize for Physiology or Medicine in 1982 for his contribution in identifying the molecular target for Aspirin and like drugs, known as cyclooxygenase. Even that was not the end of the story; few years

later, with the increasing side effect resulting from the chronic use of aspirin, another cyclooxygenase was identified and was predictably named cyclooxygenase-2 (COX-2). In this issue of *IBScientific*, Youcef Mehellou (1) reviews and evaluates the approaches towards selective inhibition of COX-2. The author indicates the common role of cyclooxygenase enzymes in prostaglandin (PG) synthesis, the ability of traditional non-steroidal anti-inflammatory drugs (NSAIDs) to ►

inhibit the activity of both enzymes. However, he highlights the distinction in the pattern of their expression and concludes that while COX-1 can be considered as a housekeeping enzyme, COX-2 is an inducible enzyme that is associated with inflammation. Additionally, structural and functional studies revealed some critical insights into COXs mode of action as well as the structural basis for their inhibitors.

The author also reports the race to develop selective COX-2 inhibitors, which were thought to be more selective with less side effects, mainly those related to gastric bleeding caused by classical NSAIDs. This race ended with the development of various COX-2 selective inhibitors some of which were approved for marketing and use. Indeed, Vioxx® (refocoxib), manufactured by Merk, showed its analgesic and

anti-inflammatory superiority compared to traditional NSAIDs and also lacking the gastrointestinal side effects typical of NSAIDs like aspirin and ibuprofen. Refocoxib was therefore a drug of choice for rheumatoid arthritis and osteoarthritis patients especially those with gastrointestinal problems, making a fortune for Merk. This fortune did not last for long though, as Merk withdrew the drug in 2004 due to other side effects such as increasing the risk of strokes and heart attacks. The author concludes by expressing the urgency for a better understanding of COX-2 pathways and strategies for inhibiting it. So certainly this is not the end of the COX-1/COX-2 selective inhibitor story. ■

(1) Mehellou, Y. (2005). *IBScientific*. 1 (2), 14-15.

And What if SoC Solution is Hidden in ... Network

Abdeljalil BENNECER
ARM Ltd.

NEUROLOGISTS, engineers and sociologists have understood for some time that studying the networks structure would help better comprehend neuronal functions, electronic components and individuals, respectively. Mathematicians, from the pioneer Euler to contemporaries, have developed some analysis tools specifically for "Graph Theory". The work of the Hungarian Paul Erdős in the sixties on the properties of chaotic networks, where edges between vertices are removed randomly, is an example in point. However, this discipline has flourished much highly in the last decade especially with advent of the Internet.

With the increasing complexity of the chip design, the need for network solution started to emerge as the most efficient solution to the challenges faced by designers. Nadjib Mammeri, Warwick University, has briefly explored the main challenges that System-on-Chip (SoC) "a complete system cast into silicon" designers have to overcome (1). He highlighted why current techniques are obsolete when 65 nm process and beyond are used. The author, then, provides different solutions based on asynchronous logic and stochastic models and gives limitations to what

could be achieved.

Mammeri puts forward the Networks-on-Chip (NoC) model, and supports on-chip micro network approach as a solution based on its maturity, similarity with other network implementation and preliminary work resulting from the works of start-up companies. Wiring delays, being the most important difficulty, will be hidden using Globally Asynchronous Locally Synchronous (GALS) method as there is no master clock between chip components while maintaining the maximum performance cost. Near the end, the author extracts differences between traditional computer networks and NoC and how could these serve to better exploit the structure.

To conclude, the author emphasises that the solution to SoC problems lies in embracing new ways to interconnecting cores together and move away from the traditional synchronous buses. With such prospect, though, many chip design companies are still reluctant to do so. ■

(1) Mammeri, N. (2005). *IBScientific*. 1 (2), 33-34.

An Engineer's Attempt to Mimic Nature

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ENGINEERING reliable, fault tolerant and yet efficient systems is the objective of every designer. However, human engineering design keeps failing every now and then. We still remember Chernobyl, Challenger, and more recently the Columbia disaster. So, now engineers are learning the basics again, by mimicking the best engineering design ever known to humans: Nature. Fault tolerance and reliability is at the heart of every biological system, therefore, designers started to bring these design techniques into digital systems (1).

Elhadj Benkhelifa, University of the West of England, introduces a new concept in digital systems design: Embryonics. Where ideas from cellular embryology are used to design electronic systems. Such multi-layered systems will virtually mimic every aspect of a living organism to achieve its fundamental features:

- Multi-cellular organisation
- Cellular division
- Cellular differentiation

The system will have the ability to self-replicate and self-repair. The idea is to establish a reconfigurable system that can self-diagnose faults. When a fault is detected, the diseased cells are rejected. Due to the limitations of the current technology, redundancy becomes a necessity and therefore spare cells will be used as a supplement to the infected cells, in order to restore the system's functionality (1).

The field is gaining interest, and proof of concept systems are being built, however the main challenge for such a novel architecture will be finding suitable applications to fit the embryonics design paradigm. ■

(1) Benkhelifa, E. (2005). *IBScientific*. 1 (2), 27-29.

Open Source Software Between the Past and Present

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Open Source Software (OSS) is software to which the source code is available under an open source license. Developers can modify and distribute OSS under the same license according to their needs. OSS compared to proprietary software (or Closed Source) is very advantageous for both, the user and the developer as well as for the software development process itself.

In an article in this issue of IBScientific, Sid Djerfi,, presented a valuable, and well structured story of the Open Source Software (Djerfi, 2005). He explained the difference between the old definition of the OSS and the new one OSD (Open Source Definition), which was proposed by Eric Raymond and his associates. The OSD, which was released by the Open Source Initiative (OSI), introduces more tolerant and commercially friendly alternatives to FSF (Free Software Foundation) - the old OSS terminology. Then Djerfi outlined the principles that underpin the OSS development process identified by Raymond. Finally Djerfi emphasized on the role of the internet to the evolution of the Open Source, and clarified the distinc-

tion between the open source and the closed source (Djerfi, 2005).

Advantages of the open source are obvious, few can be mentined: open source is relatively free, easy to evaluate, and it allows for more support options, in addition to self-support when desired, all thanks to the free access to the source code. With these advantages, Djerfi illustrated and discussed the importance of the open source paradigm over the proprietary and how it contributes to the software enhancements. ■

Djerfi, S. (2005). IBScientific. 1 (2), 30-32.

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Biology, Theory and Mathematics

Abdelkader ESSAFI

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By email

System biology is an interesting and new offspring of the mathematics biology marriage. It is a quantitative analysis of the functional interactions in a biological system with reference to time. It studies mostly change over time and uses complex mathematical and computational tools to achieve the analysis of some systems. The reductionist approach, however, relies heavily on biological data already scrutinised, and passed down the generations. It is painfully a long process, but it is extremely fitted with powerful tools to prove the same phenomenon in different ways. The data generated by the reductionist or bottoms up approach are extremely well filtered and get established very quickly. Both approaches are discovery and hypothesis driven and hence confirm to the scientific method. In most cases the two approaches are merged as system biology approach gives a clear look at the physiological consequences of the biological entity studied and the reductionist gives a clear picture about the intricacy of the entity independent of the physiological context.

Both approaches use mathematics, but system biology relies heavily if not entirely on the power of mathematics to achieve its conclusions. The second approach is a pure biological approach, because it uses "biological proofs". This difference is crucial in understanding the content of two papers published in the first issue of *IBScientific* (1,2). The authors would agree that mathematics is an important ingredient of progress in biology.

It is highlighted in the articles that the use of current mathematical tools of mathematics could be enough to model and understand biological systems or processes. That is quite a controversial view. It is



important to note that mathematical models for biological processes have been around for some time. The most renowned is the evolutionary models and game theory strategies used in animal, cellular and molecular interactions. These models were very successful in understanding some of the biological processes. The evolutionary stable strategy model, for example, introduced by John Maynard Smith was developed from mathematical basics of game theory and tailored to suit biological phenomena. Other models are worth mentioning such as the maximum likelihood score, which was tailored by Ronald Fisher to the use in biological analysis. Both of these approaches relied on a process of observation, hypothesis then experiment (i.e. the scientific method). The laws or generalisations were not proposed a priori but were inferred from biological data. Then the data support that hypothesis rather than the other way around, therefore biology benefited mathematics, and new tools of mathematics were needed for tackling biological problems. Biology also helped advance other fields of mathematics including statistics, approximation theory, game theory, chaos theory and in recent years the theory of computation.

Mathematicians when approach biology should look at biology as new inspiration where they can produce new mathematics rather than a field where they can use their already existent mathematical tools. Biology should be regarded as the new physics of mathematics. This will help

biology develop and give mathematicians new problems to tackle.

In the second paper by Mokrab, we have another issue highlighted. The definitions of theoretical, mathematical and computational biology. There is agreement that these concepts are used interchangeably but are in fact different entities as rightly explained in the article.

Theoretical biology is concerned as the author suggests with biological laws. Here a pause is needed to absorb some issues regarding the philosophy of biology. Biology has been hailed for some time as unique among the sciences, for the simple reason that predictions are scarcely right. Laws or theories, of course, lead to predictions and if predictions are wrong the laws themselves are brought into question. In this area biology is really fruitful, it never disappoints you. The so called laws are always broken and then exceptions become so numerous that the law is scratched. In genetics for example, the law of segregation of gametes is true for all sexual organisms on earth, and it has a mathematical formulae to accommodate it as well, but then it is not entirely true for some sexual organisms such as plants. Therefore, this law is always treated as a hypothesis once approached and only ►

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(1) Kaidi, A. (2005). *IBScientific*. 1 (1), 16-17.

(2) Mokrab, Y. (2005). *IBScientific*. 1 (1), 18.

the result will tell you the truth. Hence the existence of generalisations instead of laws. Physics also follow the same path but relies heavily on mathematical analysis, and the experiment is the only way to prove the theory right. Such examples include relativity theory and the eclipse of 1919, and energy relation to mass and the nuclear fission experiments in 1939.

Biology examples include natural selection theory and the breeding programmes, Kin selection theory and eusocial insects (bees and ants).

Taking the above in context, theoretical biology has always existed, but not to look for absolute laws, or law-like statement, but generalisations.

Other biologists and philosophers agree that the derivation of laws in biology is an impossible task due to different reasons including: complexity, openness of the biological systems, biological phenomena uniqueness, singularity, historicism, etc. Although most of them agree on these barriers, the debate is about the implications rather than their existence.

Theoretical Biology may never be like theoretical physics with so much mathematics involved. Mathematical biology have been taken this place and even engineers try to

mimic nature through this discipline (see Benkhilifa article in this issue) and (Rome et. al., 2005). Theoretical biology has been alive and well from the time of the early naturalists. It offers dynamic laws that are only trusted after experimentation, and they will be no final laws in biology for some time to come.

Theoretical biology is unique and to understand its uniqueness, one has to understand biological discovery and the role of theoretical and mathematical biology. An example may illustrate the point. Jacques Monod and François Jacob are credited with establishing a law in biology. It states that a protein not a gene can affect the transcription of another gene (a Transacting element induces gene expression or the operon concept). This law or generalisation - much more accurately- is still true and has never been broken, it can also be put in a mathematical formulae (Smolen et. al., 2000).

The discovery was achieved by very simple means and could be replicated in a very short time because of the use of bacterial genetics. The hypothesis was simple; if the acting element is not linked to the chromosome of the bacteria, then it can be added by external vehicles (e.g. viruses). They did the experiment while using a

gene that can be easily assayed (in this case they used an enzyme that can be tested by colour changes to the substrate). The hypothesis was confirmed hence the law cited above. This theoretical law in biology (a generalisation) and that is how theoretical biology has developed. The mathematical biology of this law as mentioned is very useful for further modelling and downstream applications.

To sum up:

System biology and reductionism work far more effectively if combined.

Theoretical biology is concerned with generalisations and the maintenance of the scientific method.

Mathematical biology is a window through which biological concepts and theories can be applied. ■

Rome, L. C., Flynn, L., Goldman, E. M., and Yoo, T. D. (2005). Generating electricity while walking with loads. *Science* 309, 1725-1728.

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The Story of COX-2 Inhibitors

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Up until late 1980s, only one form of cyclooxygenase (COX) was reported to have existed. However, in the early 1990s, this notion was changed by the discovery of a second cyclooxygenase isoform, named COX-2.

Interestingly, COX-2 was found to be associated with sites of inflammation. This observation led to hypothesise that selective inhibition of COX-2 would be an "ideal" approach for resolving some of the devastating inflammatory diseases, with less severe side effects, namely those regarding gastric bleeding caused by traditional anti-inflammatory drugs. Thus, the race was on to design, synthesise and market new selective COX-2 inhibitors. Indeed, after few years COX-2-selective inhibitors were available on the market, e.g. Vioxx and Celebrex, which had mixed fortunes with patients. This article will review the discovery and development of COX-2 inhibitors.

Cyclooxygenase has been known for a long time to mediate the biosynthesis of prostaglandins and thromboxane, via the conversion of polyunsaturated fatty acids. In 1971, Vane showed that Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), particularly aspirin, prevented the formation of prostaglandins and thromboxane by inhibiting the COX enzyme (Dannhardt and Keifer, 2001). This property of NSAIDs explained their beneficial anti-

inflammatory, antipyretic, analgesic and cardiovascular effects as well as their gastro-intestinal side effects (Marnett and Kalgutkar, 1999). Up until 1988, it was believed that arachidonic acid, the substrate for COX, was the only factor controlling the formation of prostaglandins. However, observations made by Needleman in 1988 suggested that this point of view was incorrect. He found that the amount of COX protein in inflamed tissues was significantly higher than in normal tissues. Following further studies Needleman et. al., postulated the presence of two COX isoenzymes; a so called 'house keeping enzyme' (COX-1) which is responsible for a basic level of prostaglandins, and an inducible enzyme (COX-2) which is activated by different stimuli mediating inflammatory reactions (Patrignani et. al., 2005; Needleman and Isakon, 1997). In 1991, the gene that encodes the inducible form of cyclooxygenase, COX-2, was cloned and hence its existence was confirmed. Further studies revealed that COX-1 is widely distributed in various tissues including the gastro-intestinal tract where it is believed to protect against gastric damage, while COX-2 expression is restricted to particular tissues/cells such as leukocytes where it appears to play a role in inflammation (Marnett and Kalgutkar, 1999). These suggested that selective inhibition of COX-2 could result in a specific anti-inflammatory effect while inhibition of both COX-1 and COX-2 results in undesirable gastrointestinal side effects. This theory proved that NSAIDs inhibit both COX-1 and COX-2, and a selective COX-2 inhibitor would be a good anti-inflammatory agent but unlike NSAIDs it would

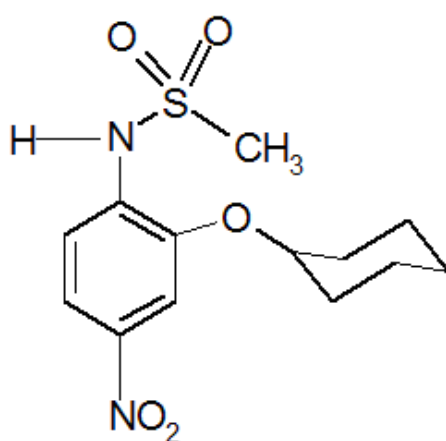
lack gastric side effects (DeWitt, 1999).

After the discovery of the COX-2 isoenzyme in 1991, it only took seven years for COX-2 inhibitors to be available on the market. This fast discovery of COX-2 inhibitors benefited from the enormous work that was carried out on the development of NSAIDs during the 1980s. Indeed, just after the discovery of COX-2, there were numerous structures available to be tested against the COX-2 enzyme. The first hint of a selective COX-2 inhibition came upon testing two compounds known as DuP697 and NS398 (Figure 1). These two compounds had anti-inflammatory activity but no gastric-effects side effects, indicating their selectivity to the COX-2 enzyme. Hence, they were the starting point of designing new selective COX-2 inhibitors.

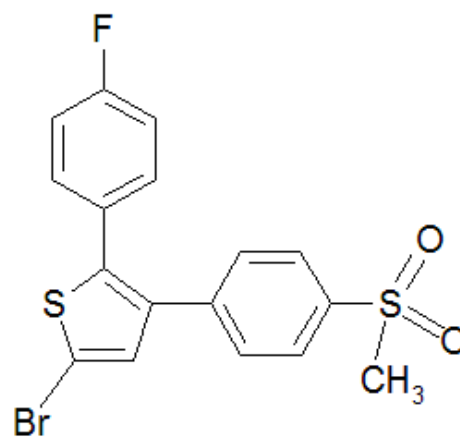
Structure activity and relationship studies of DuP697 and NS398 revealed the structural features needed for selective COX-2 inhibition. Firstly, a cis-stillbene moiety containing a 4-methylsulfonyl or sulphonamide substituent in one of the pendant phenyl rings is required for COX-2 specificity (Marnett and Kalgutkar, 1999). Secondly, The oxidation state of the sulphur in the methylsulfone moiety is required for selective COX-2 inhibition since the sulfoxides or sulfides are inactive or non-selective (Marnett and Kalgutkar, 1999). The next step was to introduce these structural features, which are responsible for COX-2 selectivity, into already known powerful NSAIDs, including Indomethacin and Aspirin. However, none of these approaches was successful.

Another breakthrough in the COX-2 ►

Below:
Figure 1: Structures of NS398 and DuP697.



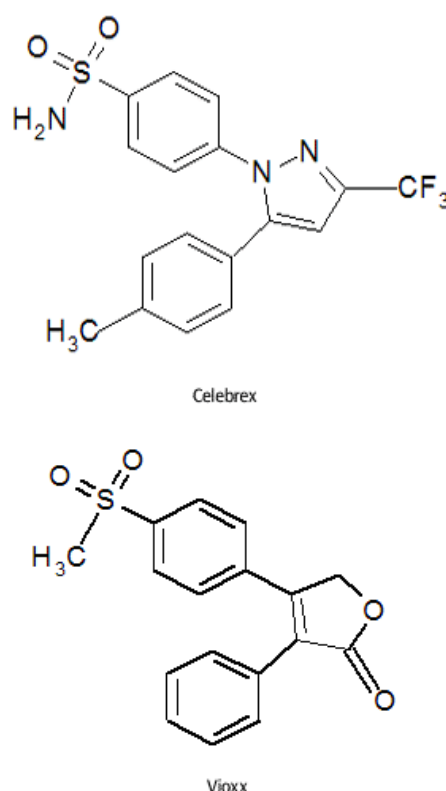
NS398



DuP697

inhibitors story came when the solution of the crystal structures of COX-1 and COX-2 became available in 1994 and 1996, respectively (Flower, 2003). This gave insights into the COX-2 selectivity of DuP697 and NS398 and, moreover, highlighted the structural differences between the COX-1 and COX-2 proteins. Although the structures were very similar, detailed examination revealed some differences that would be crucial for designing selective COX-2 inhibitors. Structural investigations indicated that the substrate binding 'channel' in the two enzymes was quite different (Flower, 2003). The presence of valine at position 523 in the COX-2, which is equivalent to a rather bulky isoleucine in COX-1, results in conformational changes that allow enhanced access to a 'side pocket' (DeWitt, 1999; Flower, 2003). This side pocket permits the specific binding of COX-2 inhibitors, as it provides a docking site for the 4-methylsulfonyl or sulphonamide groups of the inhibitors (Flower, 2003).

From this point on, the development process of COX-2 inhibitors was rapid due to the availability of selective inhibitors (DuP697 and NS398) and a good understanding of the binding site. There were no less than seven different classes of COX-2 inhibitors identified including tricyclics and acidic sulfonamides (DeWitt, 1999). One of the pharmaceutical companies that were leading the chase for a selective COX-2 inhibitor was Merck, and from their methylsulphonylphenyl series came refocoxib (Vioxx) (Figure 2). Pre-clinical investigations of refocoxib showed its analgesic and anti-inflammatory superiority compared to NSAIDs. Most importantly, refocoxib was found to lack the gastrointestinal side effects typical of NSAIDs like aspirin and ibuprofen. In addition, clinically refocoxib proved to be more effective in treating rheumatoid arthritis and osteoarthritis compared to placebo and regular NSAIDs such as diclofenac (Turini and DuBois, 2002). This encouraging data, along with the gastrointestinal safety profile, led to licensing refocoxib in the United Kingdom for the treatment of osteoarthritis in 1999 and rheumatoid arthritis in 2001. Another COX-2 inhibitor known as Celecoxib (Celebrex) (Figure 2) was licensed in the United Kingdom for the treatment of osteoarthritis and rheumatoid arthritis in 2000. Celecoxib was the first COX-2 inhibitor to be approved for use in humans. Preclinical studies indicated the significant selectivity of celecoxib to COX-



Above:
Figure 2: Structures of Celebrex and Vioxx

2 as well as its efficacy as an anti-inflammatory and analgesic agent. Human clinical studies of refocoxib in treating osteoarthritis and rheumatoid arthritis emphasised its effectiveness and gastrointestinal safety (Turini and DuBois, 2002).

Vioxx and Celebrex appeared to be the drugs of choice for patients suffering from osteoarthritis and rheumatoid arthritis and for those who have gastrointestinal problems. As a result, the concept of launching new selective COX-2 inhibitors into the market promised the manufacturers huge success. Indeed, Vioxx and Celebrex were very successful for their manufacturers as their sales reached US\$4 billion in 2000 (Flower, 2003).

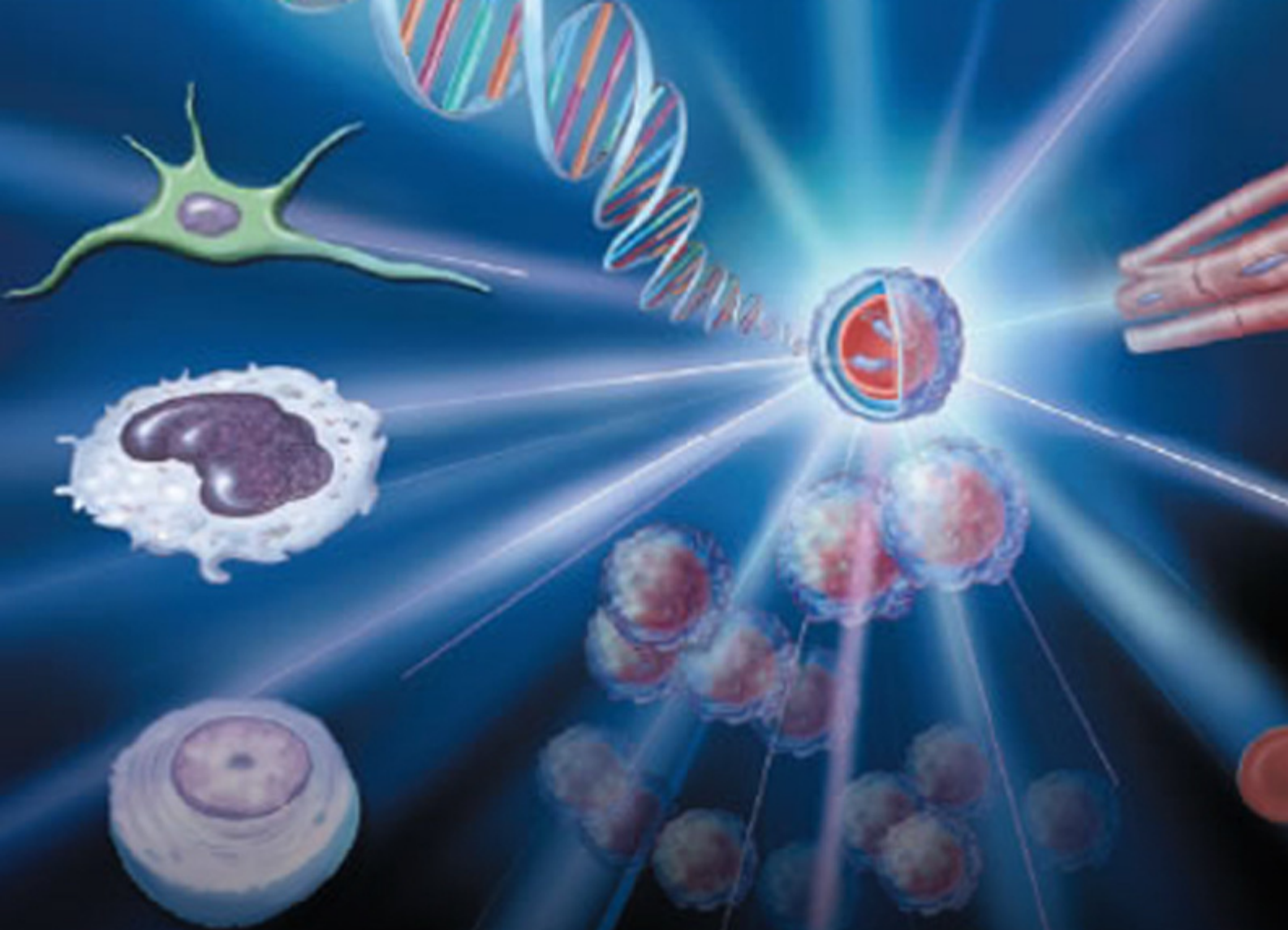
Not a long time following their introduction into the market, numerous side effects of COX-2 inhibitors were discovered. The main side effect that 'blackened' the whole class COX-2 inhibitors was their property of increasing the risk of strokes and heart attacks. This resulted in Merck suspending its blockbuster COX-2 inhibitor, Vioxx, and the FDA requesting stronger labeling for this class of drugs (Jones and Power, 2005). In addition, some scientists started to question the safety of COX-2 inhibitors and the fast track that led them into the market in less than a

decade. In fact, there were some questions about the safety of COX-2 inhibitors even before their launch into the market. For example, there was no evidence that COX-2 inhibitors will be better tolerated in NSAIDs-sensitive asthmatics (Marnett and Kalgutkar, 1999).

Although it was clear from the start that selective COX-2 inhibitors would be safer than regular NSAIDs in terms of gastrointestinal profile, and just as effective, there were still some health and safety concerns not answered. Indeed initially COX-2 inhibitors were the answer for the pain of so many osteoarthritis and rheumatoid arthritis patients. However, for others it was the start of 'new pain' from complications resulting from COX-2 intake and, unfortunately, for some patients COX-2 inhibitors spelled the end of their lives as it caused them strokes and heart attacks. This indicates that as much as we thought we knew about COX-2 inhibitors, we still have a lot to learn about them in order to make them safer for use. ■

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Stem Cells PRIMER

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Stem cell science is one of the most fascinating areas of biology today. Research on stem cells is concerned with the development of an organism from a single cell, the replacement of damaged cells in the adult organism, leading to possible cell based therapies and treatments. It entails probing the biology of these cells, and possible application of this new and upcoming technology.

Stem cell science focuses on two main issues: first, understanding precisely how stem cells remain unspecialized and retain their ability to self renew; second, identification of mechanisms and signals driving stem cells to specialize into any cell type (e.g. neurones).

As any other new technologies, there is a big misconception about stem cells. Most people believe that stem cells are always derived from the embryo; this common and widespread picture is far from being the true representation of stem cells. However, before dwelling any deeper, it is very crucial to define stem cells and their types, and enlist their characteristics.

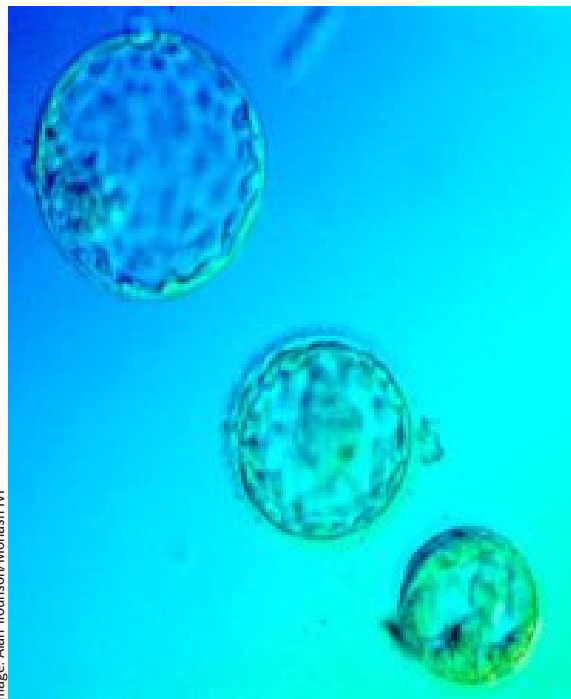


Image: Alan Trounson/Monash IVF

Left: Blastocyst Stem cells are taken from the inner cell mass of a five- or six-day old embryo called a blastocyst. These cells can grow into all the tissues of the body.

Below: The stages at which stem cells are derived.

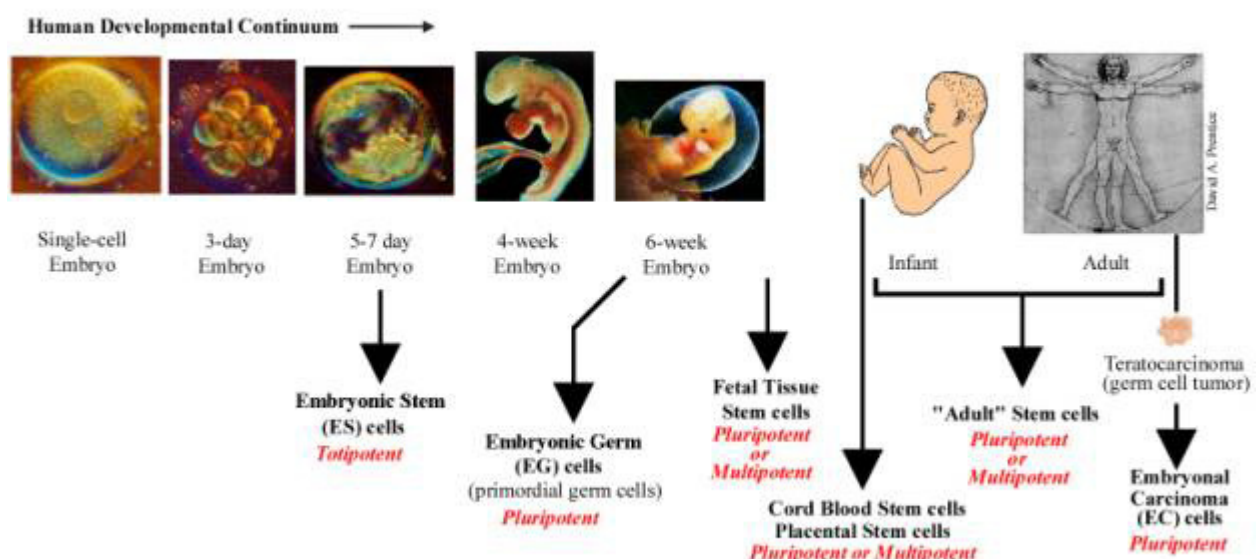
Stem Cells

Stem cells are cells that can reproduce all other types of specialised cells in different tissues and organs. Stem cells could be derived from different sources including the embryo, the foetus, and the adult organism. They are characterised by their ability to self renew for long periods of time under specific conditions.

These characteristics are shared by both adult and embryonic stem cells but they differ prominently in their ability to self renew under laboratory conditions (Smith, 2001). Embryonic stem cells proliferate indefinitely whilst adult stem cells do not.

Embryonic stem cells (ESCs)

Embryonic stem cells are derived from a group of cells called the inner cell mass, which is a part of the early four to five days old embryo also called the blastocyst. Once removed from the blastocyst, the cells of the inner cell mass can be cultured and derived into embryonic stem cells (Brook & Gardner, 1997, Doetchman, 1985). The most important take home message to remember here is that embryonic stem cells are an artefact of in vitro conditions, and there is emerging evidence that these cells do not behave in the laboratory as they would in the developing embryo (Smith 2001). In fact, the closest match for the biological behaviour of these cells in the embryo is that of germ cells (Matsui et al, 1992, Shambloott et al, 1998). The latter group of cells are isolated from the primordial germ cells of the gonadal ridge in the five to ten week foetus. Embryonic stem cells and embryonic germ cells are both pluripotent (i.e. able to reproduce all 220-cell types that make up the human body) (Evans, Kaufman, 1981, Itskovitz-Eldor et al, 2000). ►



Although the two types of cells are similar they still are not totally identical.

The process by which a pluripotent stem cell becomes specialized into a specific cell type is termed differentiation. In the laboratory a stem cell can be manipulated to become specialized or partially specialized by manipulation of different growth conditions such as: growth factors, gas percentage, and plating density. Directed differentiation is the term coined for this artificial process.

Adult stem cells (ASCs)

Adult stem cells are undifferentiated cells that reside in the adult's already differentiated tissue. They are believed to be the stock that replaces damaged cells in the tissue by virtue of differentiation (e.g. tanning for skin cells is a well documented example). In theory, ASCs still have the ability to self renew, and differentiate to the same cell type as the tissue they reside in. At present, however, there is no isolated population of adult stem cells that can differentiate to all kinds of cells in the body.

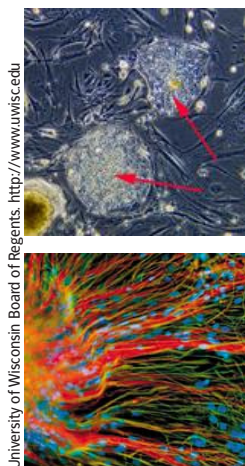
This can be partly explained by the fact that adult stem cells are rare and very difficult to isolate and purify, and also to their inability to replicate or self renew in culture conditions outside their physiological environment in the body.

The stated limitations do not stop us from exploring other features of these cells. Plasticity is a very exciting characteristic of adult stem cells. It is defined as the ability of an adult stem cell from one tissue to generate the specialized cell type of another tissue (Bjornson et al, 1999, Alison et al, 2000). Plasticity of these cells is a very new phenomenon that is still not thoroughly understood and under continued investigation. Adult stem cells also have another feature that sets them apart from ESCs. It is the fact that their physiology and biology are preserved in vitro as in the tissues they originated from.

Comparison Between Adult Stem Cells and Embryonic Stem Cells

Most concerns about stem cell research arise from the use of human embryos for their production or generation and the potential waste of a human life. Therefore, many actually propose the use of adult stem cells as an alternative to embryonic stem cells, because of less controversial issues associated with them.

It is a fact that adult and embryonic stem cells share many characteristics. They both have the ability to self renew and give rise to specialized cells. They are isolated in an undifferentiated state, and can proliferate and differentiate upon transplantation into immunodeficient animals. They further share the capacity of homing to the site of injury after transplantation, and being influenced by cellular and non-cellular conditions regulating their differentiation



Top:
The red arrows point to embryonic stem cells growing in a petri dish.

Above:
Derived from human embryonic stem cells, precursor neural cells grow in a lab dish and generate mature neurons (red) and glial cells (green), in the lab of UW-Madison stem cell researcher and neurodevelopmental biologist Su-Chun Zhang.

(Guenechea et al, 2001).

In spite of all these similarities, scientists are still not very optimistic as adult stem cells are limited in their potential to differentiate into all different cell types of the body. They are also concerned with the prospect of mass production as ASCs lose their potency readily over time. Having said that, adult stem cells still represent the best therapeutic option for certain diseases.

For example, transplanting adult stem cells isolated from umbilical cord into anaemic or haemophilic patients is becoming a routine procedure. Unlike ESCs, adult stem cells do not form a teratoma form of benign tumours as embryonic stem cells do upon transplantation.

Future Applications of Stem Cells

Regenerative medicine

This new and dynamic area of therapeutic medicine will benefit great deal from advances made in human stem cell research. Stem cells can be used to replace lost or damaged cells or tissues in many devastating conditions such as Parkinson's, diabetes, chronic heart disease, end stage kidney disease, liver failure and cancer (Gage et al, 1995a, Gage et al, 1995b, Shihabuddin et al, 1999).

Recent advances in the field, for instance, lead to the development of pancreatic tissues that can be used to treat diabetes, and lead to the derivation of insulin producing cells from human embryonic stem cells (Zulewski et al, 2001, Lumelsky et al, 2001). These advances can be translated into therapeutic use by transplanting these cells into the patient.

On the other hand, the mass media played a big role in spreading some misleading statements about the advances of stem cell use in regenerative medicine. The common understanding is that stem cells can be used in regenerative medicine in the very near future, giving false hopes for patients. In fact the reality cannot be more different. Neither embryonic nor adult stem cells are ready to be used in such therapeutic applications. Embryonic stem cells need directed differentiation to specific cell types before transplantation, which is in a matter of fact very daunting and difficult task as explained by the limitations presented by the two cell types.

Therapeutic delivery system

Another application for stem cells is therapeutic delivery system, where stem cells are used as vehicles for delivering genes to specific tissues in the body. This approach will be more used in treating cancer, where specialized cells are designed to target specific cancerous cells and directly deliver agents to destroy or modify them.

In addition to these applications, stem cells in the future will be used to explore effects of chromoso- ►

mal abnormalities in early development and test candidate therapeutic drugs and develop specialized liver cells to evaluate drug-detoxifying capability.

Current Challenges and Advances of Stem Cell Research

Isolation and growth condition

Stem cell science is facing many challenges, especially difficulties in isolating and defining growth conditions for stem cells in vitro. This is clearly illustrated by the fact that although mouse embryonic stem cells were derived in 1981, it took nearly twenty years for James Thomson to derive the first human embryonic stem cell line in 1998 (Thomson et al, 1998).

Defining the conditions for directed differentiation of embryonic stem cells into different specialized cell types is still a daunting task, let alone finding ways to control their development or proliferation after transplantation into patients.

Immune rejection

The immune system recognizes cells and tissues that are not defined as "self" and mounts a rapid response, which consists of an attack on the graft (transplant). This response could be rapid and strong (acute), or sustained for long period of time (chronic), however the end result in both cases is the same, the loss of the graft.

A much better way to overcome immune rejection without leaving the patient prone to infections is to perfectly match the donor and recipient, which can only be achieved between identical twins. Because of such constraints, stem cells can be safely transplanted if they are derived from the patient who will receive the transplant, or must be engineered to overcome immune rejection. Currently, the most promising technique to overcome this problem is nuclear transfer; the grafted embryonic stem cells are loaded with the patient's DNA. These cells are genetically identical to the patient's tissues and hence are recognised by the immune system as one of their own.

Another approach to avoid immune rejection consists of destroying the patient's own immune system and replacing it with immune cells from the organ donor prior to organ transplantation. However, this approach is very dangerous, has a low rate of success, and it takes a long time to establish the new immune system. The patient in this period is vulnerable to infections due to the absence of a complete and functional immune system.

Consequently, nuclear transfer seems to be the most attractive option. The technique used in nuclear transfer is a routine procedure in some laboratories, where the DNA from any one cell in the body, usually the skin cell, could be removed and transferred through a microscopic glass tube into an unfertilized egg that had its own DNA removed. The egg is coaxed into developing by providing the necessary conditions and requirements (it is the exact technique used in reproductive cloning that produced Dolly, the sheep). After few days of development, a blastocyst is formed. As mentioned earlier, stem cells are derived from the blastocyst's inner cell mass, and further manipulating the cells to generate cells and tissues for the patient (see Shufaro & Reubinoff, 2004 and references therein for a review).

In March 2004, a South Korean research team reported that the first successful establishment of human embryonic stem cell line after nuclear transfer of somatic (non-reproductive cells) DNA into a human egg. The resultant cells were a perfect match for the donor individual (Hwang et al, 2004). This made treatment for diseases like diabetes very realistic by transplanting insulin-producing cells from the established human stem cells, and by manipulation of conditions the cells can be tailored to the patient, without possibility of rejection.

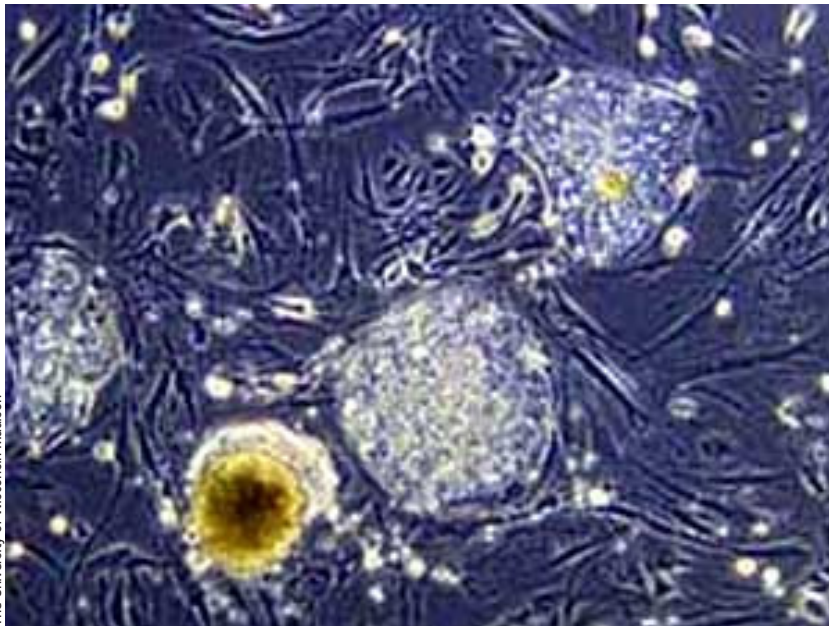
Although, this report is considered a milestone in the field, there are still many hurdles to overcome. The efficiency of derivation of embryonic stem cells was very low in comparison with deriving human embryonic stem cells from normal fertilized eggs. The actual rate was only 30 out of 242 nuclear transferred eggs gave rise to blastocytes, and further more, only one of these thirty blastocytes could be used to derive human embryonic stem cell line.

Another major fear is that these nuclear transferred human embryonic stem cells are cancerous which ►

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The University of Wisconsin-Madison

Above:
A microscopic view of colonies of human embryonic stem cells being studied in a University of Wisconsin research lab. The colonies are the rounded, dense masses of cells.

was observed in some animal model (e.g. Dolly the sheep).

Animal product contamination

One of the big concerns for using stem cells in therapeutic transplantation is the use of animal products in the different processes for stem cell generation, derivation and manipulation. The use of animal products may lead to contamination of the derived human cells with viruses and pathogens from animal cells, and consequently transmission to the patient receiving the treatment.

Scientists at the Roslin institute in Edinburgh had some way around this problem. Dr Paul de Souza and his team derived the first human embryonic stem cell line without a direct exposure to animal products by using a layer of human protein called Laminin instead of animal compounds as a growth matrix on which, human embryonic stem cells were growing, and used neonatal foreskin cells to provide nutrients and growth factors instead of mouse feeders. To eliminate the use of bovine growth factors, they resorted to the use of human growth factors and proteins. This procedure was not completely animal product free, because the foreskin cells used were exposed to animal products during their derivation. In spite of this, the contact with animal product is not only indirect but also considerably reduced and it is a very important contribution to the advance of the field of stem cells (see De Sousa et al, 2004 for a review).

Heterogeneity of transplanted stem cell populations

Another big issue facing the use of stem cells in therapeutic applications is the heterogeneity of the stem cell populations used for transplantations. Heterogeneity is the presence of different types of differentiated cells derived from a single stem cell. Embryonic stem cells can give rise to a mix of differentiated population causing teratomas when transplanted, thus pure populations of progenitor or pre-

cursors of a specific cell type are needed. This path in the field has been very unsuccessful, till very recently.

On the 17th of August 2005. Scientists at the institute for stem cell Research at the university of Edinburgh and Milan reported the derivation of the world's first pure population of nerve stem cells derived from human embryonic stem cells (Conti et al, 2005). This discovery not only shades light on how to produce a homogenous population of cells but opens wide doors for proper therapeutic usage. Dr Steven Pollard is one of the first authors of this report; and in an interview he said that it is incredibly exciting in terms of curing diseases such as Parkinson and Alzheimer's. However, it is still a long-term aim for these cells to be used to build replacement neural tissue, but the more immediate use for the artificially created cells is to test out the effectiveness of new drugs. The latter use is an incredibly important pillar of drug discovery. These cells can also be used in disease staging especially for developmental diseases such as Leukaemia or diabetes. Dissecting the different stages of disease development and evolution can help unearth ways to combat the disease.

Stem Cell Research Under Scrutiny

Only in the last twenty years, stem cell research has made huge steps and is still advancing in a very fast pace. However, there are huge issues needed to be solved before rushing into clinical applications or trials. Looking at the different applications already cited, we can see this picture more clearly.

In fact most evidence of regeneration comes from mouse stem cells. The results cannot always be translated as direct evidence for understanding human embryonic stem cells. Furthermore, stem cell research is too dependent on in vitro manipulation of conditions, which can be in fact artefacts and may not represent the real scenario in the body. In fact relatively subtle changes in culture conditions can have dramatic influences on the type of cells that develop.

Adult stem cells face other serious issues as well. The plasticity of adult stem cells may be due to the presence of different populations of stem cells in the isolated cells. Here the clonality issue is very difficult to tackle but, is very crucial in understanding the nature of these cells. Plasticity could be a result of cell fusion between the injected adult stem cell and the cell type of the host tissue, fusion is the melding of two or more cells into one cell called a heterokaryon (a cell with two separate nuclei formed by the experimental fusion of two genetically different cells). A heterokaryon may reproduce itself for at least several generations, and in the case of fusion between an undifferentiated stem cell and a mature differentiated cell, the resultant cell can retain the mature cell phenotype. ►

There are still more crucial issues related to stem cells. Do adult stem cells exhibit plasticity as a normal event in the body or is it an artefact of the culture conditions?

How many kinds of adult stem cells exist and in which tissue they reside?

What stage of differentiation of stem cells will be best for transplantation?

In addition to all the questions about the basic science of stem cells, what are the mechanisms of self-renewal? What are the signals leading to differentiation of every single cell type? And many more.

Finally I am left with one thought in my mind, is it appropriate to worry about all the ethical issues, where we still don't know the answer to many and many questions?

Or is it at all possible to decode the secrets of life? ■

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Stem Cells and Parkinson's

Dr Steven Pollard from the Institute of Stem Cells Research, Edinburgh, explains.

In the next pages there is an interview with Dr Steve Pollard, the author of new discovery published recently in *PLoS biology*. This journal is very highly respected open access journal with an impressive first impact factor, that welcome original research in biological science.

The study was about finding growth factors that can determine the development of Stem cells into functional neurones in non-physiological setting (i.e. in the lab). The work was done in Professor Austin Smith lab, one of the prominent researchers in stem cells in the world and an authority on self-renewal in stem cells. This new discovery is one

of many that have been published through the years in the lab.

Stem cells in the body develop into neurones in the embryo, but the growth factors responsible for this directional differentiation eluded discovery till now. Fibroblast growth factor 2 (FGF-2) and epidermal growth factor (EGF) were shown to be enough to direct such a transformation, and that the loss of any of them will result in cell death (apoptosis). FGFs are known to be involved in the regulation of neuronal development as testified by mouse models, but EGFs are not that studied.

This study therefore not only provides a guinea pig for neuronal research, but makes the possibility of tackling new questions in different fields certain such as: signalling research, cytokine research, neurosciences, developmental biology, therapeutic medicine and stem cell research.

This however is only the tip of the iceberg as our understanding of the ES biology is still at its basic and new evidence suggest lots of limitations for this type of work (Maitra et al., 2005). ■

Maitra, A., Arking, D. E., Shivapurkar, N., Ikeda, M., Stastny, V., Kassaei, K., Sui, G., Cutler, D. J., Liu, Y., Brimble, S. N., et al. (2005). Genomic Alterations in Cultured Human Embryonic Stem Cells. *Nat Genet*.

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How to Make Nerves in a Petri Dish?

Interview taken at Institute of Stem Cells Research, Edinburgh University, 18 August 2005, by
Fella ESSAFI
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IBS: Before we start, we congratulate you for your work published on PLoS biology,

1. IBS: How did you get into stem cell research?

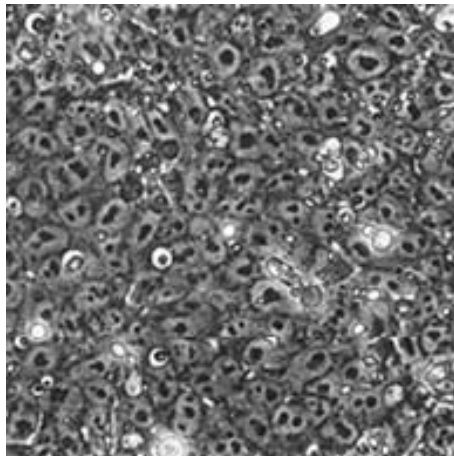
My undergraduate degree was biochemistry, and I realised that although an interesting topic, I would like to learn more about cell biology and especially developmental biology, as this seemed to be a field in which great progress had been made during the 80s and 90s. So I did my PhD at NIMR in London on the topic of zebrafish development. My supervisor there was the first person to isolate neural crest stem cells when he was a PhD student in the states. So I got interested in the topic through conversations with him, and also, of course, because human stem cell lines had just been isolated, which is a massive landmark in the field. Also, I felt my background in biochemistry, molecular biology and developmental biology was a good training to move into this area.

2. IBS: Why ISCR and the group you are working in?

Austin Smith realised quite early on that ES cells are a fascinating type of cells. He was one of the pioneers of ES cell research and has been working on mouse ES cells longer than almost anybody else in world. So, Edinburgh, and Austin's lab was really by a long way the best place to go to work on this problem of what stem cells are and how we can control them.

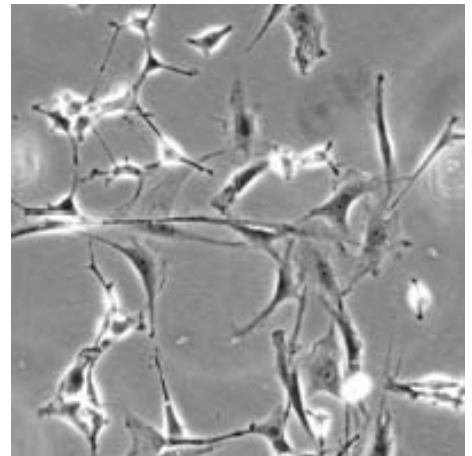
3. IBS: The discovery you made recently is about making neuronal stem cells in a test tube and maintaining their capacity. Can you talk us through the ups and downs of this story?

The work I did recently, together with another PostDoc in the lab Luciano Conti, involved trying to convert ES cells, which can make every cell type in the body, into a more restricted tissue stem cell, namely a neural stem cell, that can only make brain and spinal cord cell types. Luciano and I were both able to get cell lines coming through, but we did it in very different ways, I had made clonal cell lines while Luciano was expanding out populations from ES cells. For a while it looked as



Above:

A colony of embryonic stem cells. These cells can make all the cells in the human body including neural stem cells.



though we had completely different cells. Because he sat right next to me in the office we also discussed and compared results. We realised with a few simple experiments that in fact we were working with the same type of cell. They were quite easy to isolate and grow with our methods so it became interesting to find out what these cells are and whether they would be useful. I found pretty quickly that they looked like they might be radial glia - and then soon after Luciano made the key discovery that they can make neurons. So it all fitted together very nicely, we both had different ways of obtaining the same cell type, and these cells were very similar to normal embryonic cells that generate the nervous system - the radial glia. Within 6 months we found you could get the same cells from any ES cell line or foetal brain, and then within a year that similar cells can be isolated from human ES cells and human foetal brain.

4. IBS: How long did this work take?

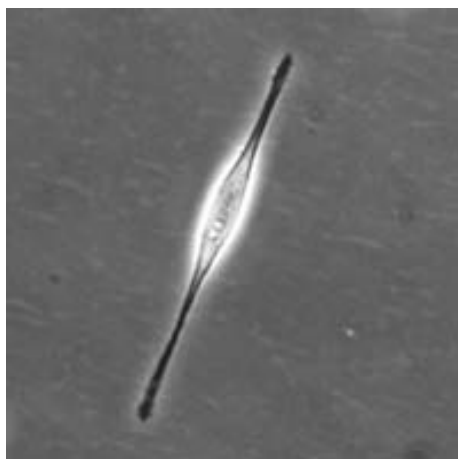
Most of the work was done within 1 year, which is pretty quick for science. But it took another year then to really finish off and fully characterise everything.

5. IBS: The discovery was firstly made in mouse ES cells, and then repeated in Human ESC. What was the main difference between the two models?

There aren't too many differences between the mouse and human cells, which is why we rely so heavily on mouse studies in the lab - they tell us a great deal about human biology. The major obvious difference when you work with each cell line is that the human cells grow very much more slowly than mouse cells. This is also the case with ES cells and reflects the fact that mice are born within a couple of weeks after fertilisation - whereas humans take 9 months.

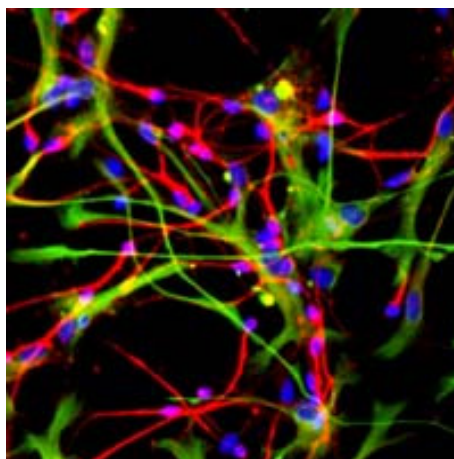
6. IBS: In the paper published in PLoS biology, you stress the niche independence of these cells. Why is this important?

Niche independence, really means the cells can be grown in a simple environment. In fact they grow on just plastic with some basic nutrients and two key protein growth factors. They can also grow up in isolation from one single cell. People grew neural stem cells in a 'dirty' way before in which they grew as big clumps of cells in suspension. We found a simpler way to grow them, which revealed there was nothing vital to their growth within this clumpy environment. Also by growing them in this way we found that the stem cells stay very pure, and do not specialise or differentiate into mature cell types. This is important as we can now study the basic biology of these cells much more easily in the lab to try and find out what ►



Above:

A single neural stem cell can make all the cell types of the nervous system like neurons (red) and astrocytes (green), in the adult brain.



makes them this special type of stem cell.

7. IBS: How do you think this discovery will shape research in the field?

Hopefully people will follow our methods and work more with these pure stem cells. A lot of confusion reigns within the field because of the unreliable way in which people grow neural stem cells at the moment. The second point of the study, in fact the initial aim, namely the conversion of ES cells into neural stem (NS) cells, should be a step forward in understanding how to make whatever brain cell type we like in unlimited numbers.

8. IBS: Does this discovery open a window for the production of other tissues in the dish to model disease?

It doesn't directly tell us how to grow up other types of tissue stem cell, such as a skin stem cell or blood stem cell. However, it is hopefully a proof-of-principle that may inspire others to test similar approaches.

9. IBS: Embryonic Stem cells are the next big thing in the Pharmaceutical industries, do you think this discovery will speed the use of these cells and relieve the subject from ethical concerns?

Hopefully the cells will become useful to try and identify new and better drugs to treat certain diseases of the brain. Also, the cells may well help us understand certain types of brain cancer, which is in essence a type of stem cell disease. This is one area we will focus on in the future. Our interest as basic scientists will be to use the cells to understand how stem cell work and why they are special. The beauty of science is that we really can't predict exactly where things will go, but the over-

all trend is clear that in a few decades we will be able to make unlimited quantities of certain cell types in the dishes. This will revolutionise our understanding of how the body works and how we can repair or replace tissues during disease processes or aging. The ethical concerns will always be there as they are largely dominated by certain religious views.

10. IBS: Any advice for biologists and scientists?

Work on something you are interested in and read a lot.

IBS: Thank you for your time Dr Pollard, and very good luck for the future. ■

Notes to the Reader (From the Original Press Release, 17 August 2005)

The Institute for Stem Cell Research (ISCR) is a multidisciplinary research institute focused on molecular, cellular and developmental biology of stem cells. The ISCR's mission is to acquire an understanding of the mechanisms of stem cell self-renewal and differentiation processes and to provide scientific foundations for the application of cell replacement therapies in the treatment of human disease and injury. Further information on the ISCR is available at www.iscr.ed.ac.uk.

EuroStemCell is a four-year Integrated Project of the European Union's Sixth Framework Programme, and will receive up to €11.9 million in funding from the EU. The 24 participating laboratories are from Scotland, England, Sweden, France,

Denmark, Italy, Germany, and Switzerland. They comprise universities, research institutes and 3 biotechnology companies. EuroStemCell's mission is to build the scientific foundations required to take stem cell technology to the clinic. Further information on EuroStemCell is available at www.eurostemcell.org

European Union's Sixth Framework Programme (FP6). The Framework Programme is the main European instrument for research funding in Europe. FP6 aims to contribute to a true 'European Research Area' (ERA). At the Lisbon summit in March 2000, EU governments called for a better use of European research efforts through the creation of an internal market for science and technology – a 'European Research Area'. FP6 is the financial instrument to help make ERA a reality.

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Stem cells glossary

Stem cell - unspecialized cell that has the ability to multiply without limit, and can also give rise to specialized cell types in the body.

Embryonic stem cell - Stem cell originating from the early embryo that has the potential to make most cell types both in the body and in the laboratory.

Neural stem cell - Stem cell found in the brain. Has the ability to make all the different cells of the nervous system: neurons, astrocytes, oligodendrocytes.

Adult stem cell - Undifferentiated cell found in a specialized tissue (i.e. bone marrow, skin, muscle etc.). Has the ability to make a limited range of specialised cell types.

Is There a Role for Steroids in Reducing Traumatic Brain Injury Morbidity and Mortality?

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Traumatic brain injury (TBI) remains a leading cause of death in the under 45 age groups. Although only 5% are classified as severe, they still represent a major cause of disability and economic cost (Kay & Teasdale, 2001). This burden has prompted a huge need for new therapeutic approaches to combat TBI as well as an assessment

of existing treatment. ple, a 1996 British survey of 39 surgical intensive care units found that 49% were using corticosteroids (Jeevaratnum & Menon, 1996), with much higher statistics in the USA, where 64% of trauma centres used the drugs in 1995 (CRASH trials collaborators, 2004). The others were more sceptic of the use of these drugs due to the confusing scientific literature available.

With the surprising results of the largest ever corticosteroid study revealed recently, are steroids going to be withdrawn from the management of severe head injury?

With the surprising results of the largest ever corticosteroid study revealed recently, are steroids going to be withdrawn from the management of severe head injury?

of existing treatment.

With better understanding of the pathophysiology of severe head injury, there have been dramatic advances in its management, which not only led to a reduction in the mortality but also a remarkable improvement in the outcome of head-injured patients. Due to the lack of appropriate models for this trait, most of the knowledge about it is gained from patients, which limit the feasibility of discovery and proper understanding of the pathology. Therefore, identifying an effective treatment is still the big challenge in trauma research.

A number of treatments have been deemed to have an impact on the outcome of patients with severe head injury, and steroid use is one that has for a long time been controversial, with scientific evidence debating clinical practice (BTF, 1995). This case is by no means the exception as our knowledge of some diseases is very restrictive.

Different effects have been associated with steroid administration in these cases leading to a substantial variation in their use by clinicians around the world. For exam-

We start with the pros and cons of corticosteroids to establish a coherent picture about their effectiveness in the medical literature.

Evidence For Corticosteroids Effects

The first evidence of the usefulness of corticosteroids in TBI was amassed from case study reports and some early clinical trials suggesting a beneficial outcome for the use of these drugs. Further understanding of the TBI biology created the infrastructure for their use. The rationale behind the use of steroids lies in the pathophysiological events of traumatic brain injury. Head injury is a staged process that encompasses primary assault at the time of injury in addition to secondary brain damage. These injuries invoke a cascade of intracranial inflammation and disrupted cerebrovascular auto regulation, leading to increased intracranial pressure (chest-

nut et al, 1993). This model is widely accepted and it supports the role of steroids as anti-inflammatory drugs.

Since Galcich and French reported a significant improvement in 28 out of 34 patients who received corticosteroids for cerebral oedema in 1961, the use of corticosteroids has been widespread. Steroids have been advocated to ameliorate intracranial inflammation and reduce intracranial features, which are cardinal features of severe head injury (Alderson & Roberts, 1997).

Alongside these lines, further work on mice consolidated the effectiveness of the drugs. Hall showed that high-dose methylprednisolone can reduce post-traumatic neuronal degeneration and enhance recovery in mice who have been subjected to severe brain injury (Hall, 1985). This study supports the role of steroids in the treatment of TBI and presents a possible mechanism for their cellular mode of action. On the other hand, the mice used do not recapitulate TBI symptoms in all cases and show at the possible effectiveness of the drug in a subset of TBI patients. Early and continuous administration of corticosteroids was also supported by other animal studies. These studies suggested that there may be an initial reversible phase of neurological deficit following head injury, which can be targeted by steroids (Kostron & Russeger, 1990). This window of therapeutic opportunity before the neuronal generation is irreversible and, though easily measured in mice, is very difficult to pinpoint in patients given the speed of deterioration. Due to the suggested limitations, these findings were never proved nor replicated in patients (Teasdale, 1991).

On the other hand, another approach can be applied to patients, where patients are treated with the drugs and outcomes are recorded for analysis or what is termed as a clinical trial. In support of experimental studies, a number of clinical trials have been carried out over the past two decades to evaluate the use of corticosteroids in traumatic brain injury. In a prospective, double blind multi-centre clinical trial of 396 cases in Germany, steroid administration was shown to be beneficial for patients with severe head injury, both reducing their mortality and promoting their recovery. In keeping with the ►

These studies (The US national acute spinal cord injury study) add weight to the role of steroids in the treatment of traumatic injuries

Steroids can inhibit certain molecules that are important for mucosal regulation, and hence the absence of the mentioned side effects gave mixed signals about their role in TBI.

results from animal studies, immediate and early use of steroids at the scene of injury was therefore recommended (Grumme et al, 1995).

The role of steroid use was also re-addressed when they were found to improve the outcome of acute spinal injury at 6 months. The US national acute spinal cord injury study examined the effect of 24-hour corticosteroid therapy on patients who suffered a spinal injury and found a greater improvement in the motor and sensory functions at 6 months. The results were replicated in other trials, with an emphasis on better outcome with 48-hour than 24-hour treatment (Bracken, 1999). These studies add weight to the role of steroids in the treatment of traumatic injuries.

In order to get a much clearer idea about the meaning of different clinical trials, a synthesis of the data was needed. A meta-analysis of all randomised controlled trials of steroid use in severe head injury was carried out by Alderson and Roberts in 1997, who suggested possible benefits from steroids (hazard ratio for death = 0.91), but the 95% CI was from 6% fewer to 2% more deaths). This meta-analysis was inconclusive but formed the basis for the largest ever trial shortly described (Alderson & Roberts, 1997). The above studies lack the statistical credibility of clinical trials and are therefore partially conclusive at best.

Evidence Against Corticosteroids

Although impressive reductions in mortality and morbidity in experimental studies have raised high expectations for the use of corticosteroids in severe head injury, a number of clinical trials have challenged their effectiveness.

The use of high-dose corticosteroids was studied in a double blind controlled trial of 161 patients conducted over a 3-year period, and the study reported no advantage of high dose dexamethasone on the intracranial pressure or the clinical outcome of the patients (Dearden et al, 1986). A poorer 6-month outcome was observed in patients with elevated intracranial pres-

sure who received steroids, but no increase in pulmonary, gastrointestinal or other extracranial complications. Steroids can inhibit certain molecules that are important for mucosal regulation, and hence the absence of the mentioned side effects gave mixed signals about their role in TBI.

Nonetheless, it can be argued that this trial and all the previous randomised controlled trials for the use of steroids in severe head injury have been too small to demonstrate reliable clinical benefit or harm. Therefore, a need for larger samples was building in order to give more conclusive outcomes. The largest trial included only a few hundred and all together about 2000 patients, which led to the inconsistency in the use of steroids in head injury. However, the newly released final results of the prospective multi-centre CRASH trial (Corticosteroid Randomisation After Significant Head injury), looking at the effects of a 48-hour infusion of corticosteroids on death and neurological disability in head injured adults, have finally put an end to the uncertainties surrounding the clinical effectiveness of steroids on severe head injury.

Given the global public health importance of head injury, the trial recruited 10,008 patients from over 200 hospitals in 50 countries. The trial was halted due to the apparent harmful effects of steroids (CRASH trial collaborators, 2005). Outcome at 6 months was obtained for 96.7% of patients, and the risk of death was significantly higher in patients receiving corticosteroids compared to the placebo group (25.7% vs. 22.3%; hazard ratio = 1.15, 95% CI = 1.07-1.24, $p = 0.0001$). The risk of death or severe disability was also found to be higher in the corticosteroid group (38.1% vs. 36.3%; hazard ratio = 1.05, 95% CI = 0.99-1.10, $p = 0.079$). As seen from the results, although the difference is around 2%, it is still statistically significant. With regard to possible confounding factors such as severity of injury and time from injury to administration, there was no evidence that they would influence the outcome. These final results confirm the previous findings reporting the risk of death at two weeks after injury, which also led to refuting routine corticosteroid use in head injury (CRASH trial collabora-

tors, 2004).

The cause of death in those patients remains to be fully investigated. It was suggested that there is likelihood for corticosteroids to induce hyperglycaemia (Douglas, 2005). The precise contribution is unknown, but it is important to remember that hyperglycaemia is common in severe head injury with or without the administration of corticosteroids. The dexamethasone study conducted by Gaab MR et al showed that 30% of the patients in the placebo group were hyperglycaemic compared with 48% of the dexamethasone group (Gaab et al, 1994). A further attempt to explain the deaths of patients receiving corticosteroids in the CRASH trial was made by Anna Kasperlik-Zlуска and colleagues. Their hypothesis suggests that corticosteroids invoke a secondary adrenal insufficiency due to suppression of corticotrophin-releasing factor and adrenocorticotrophic hormone by the high doses of methylprednisolone used (Anna et al, 2005). They added that adrenal insufficiency, possibly explaining the deaths, can be potentially corrected by a routine 7-10 days replacement therapy (Anna et al, 2005). In the absence of sufficient information on concomitant extra cranial injuries, clinical course and interventions; it is difficult to ascertain the exact cause of death of the CRASH trial patients.

The jury is still out there for the causes of deaths and still further work to be done to establish if the cause can sufficiently be linked to steroid use. However, it is clear that the use of these drugs does not show any beneficial effects on patients and in some cases has fatal consequences, hence the halt of the study.

Do Steroids Heal or Harm Head-Injured Patients?

In summary, based on current evidence, steroids have no place in the management of severe head injury. In fact, their contribution to mortality is a strong possibility that needs to be explained.

It is fair to conclude that the CRASH trial was a breakthrough in the history of steroid use in severe head injury. The reliable demonstration of their potential harm leads to definite refutation of their use in severely head injured patients. Corticosteroid use should also be re-evaluated for other indications particularly ►

acute spinal injury.

For the time being, other more direct interventions are needed to get the patients the best outcome. ■

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Self-Repair and Self-Healing...

Biologically Inspired Hardware Systems for Improved Fault Tolerance and Reliability

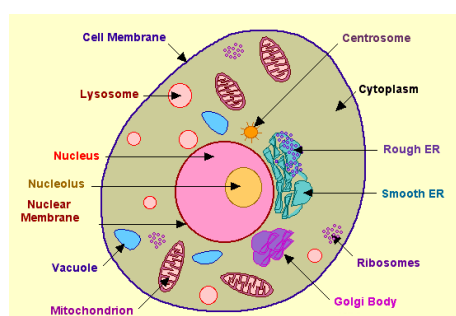
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Nature continues to inspire man kind with some amazing and very complex structures and behaviours, especially in living organisms. Biological organisms, for instance, involve highly complex features and behaviours through a miraculous and well organised cooperation of a huge number of principle actors called the cells. In this research article, my plan is to evaluate and apply novel, biologically inspired processes and algorithms for implementing a reliable VLSI systems on silicon with self-diagnostic and self-healing mechanisms, which are offered by the biological organisms. Such systems, similar to their biological equivalents, will possess cellular architecture properties with self-repair mechanisms, Embryonics (embryonic electronics), the fault tolerance property; Immunotronics (immunological electronics), and will aim to meet the needs of any real-time applications. In this article the field of Embryonics is addressed.

Reliability has been a key word and one of the biggest challenges since the beginning of life. Therefore almost everything is assessed by its reliability. The world of digital electronics certainly cannot escape this matter, especially when powerful and sophisticated systems have become the necessity of the modern life. From a certain viewpoint, the modern world of digital electronics; virtually all of which is now built using VLSI (Very Large System Integration) technology; is rather brittle edifice. In order for any VLSI system to carry on operating without malfunction we are quite accustomed to the idea that hundreds of thousands, often millions, of individual active electronic components on the chip must work together faultlessly over extended periods of time. Yet it is sufficient for a single transistor to fail to have catastrophic consequences for the entire system.

Reliability issue in electronic systems grows with the actual complexity they create. The more complex the system becomes, the rapid the reliability is hindered (Sipper et. al., 2005). Building such dependent and consistent electronic systems and guaranteeing their fault-free or at least fault-tolerant performance at all times and under all reasonable conditions to assure constancy, quality, and adequacy is not a straightforward task; particularly in sensitive circumstances, for example anti-lock braking systems and control system at nuclear power stations, in which,



Above:
Figure 1: An example of an animal cell (Animal Cell Anatomy, 2001)

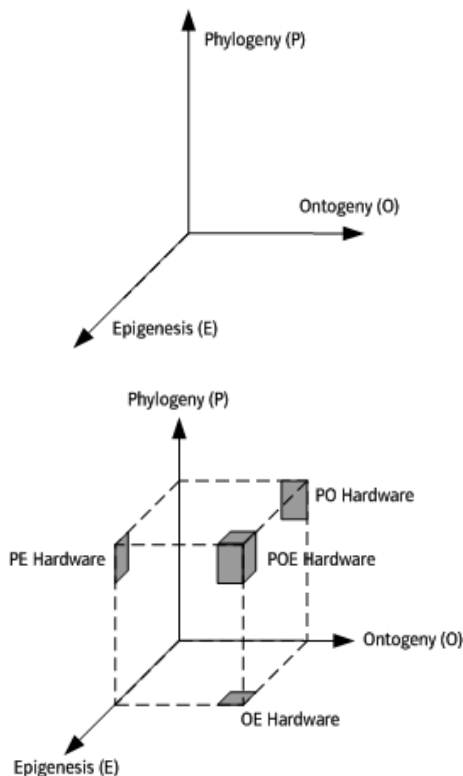
accurate functions must be in place for extremely hazardous consequences to be avoided. Therefore the presence of fault-tolerant mechanism in an electronic system is vital in order to be a safety critical one. So how can we implement such a reliable system?

The human body is a remarkable example that inspires researchers towards bio-inspired hardware systems since it is considered to be one of the most complex yet highly reliable systems. It consists of roughly 60 trillions cells, all of which has started from the stem cells to be functionally specialised as a result of division and differentiation processes in the embryological phase; producing liver cells, skin cells, defence cells,... etc. The efficient interactions between these cells make the biological system one of the most complex system ever known to man kind. Failures in living organisms such as the human body are common due to the continuous

invasions of pathogens. However, almost in all cases, faults are detected and healed thanks to the self-diagnostic and self-repairing mechanisms resulting in high reliability. This demonstrates how nature deals with the increased complexity and reliability problem. Nature achieves the high level of functional integrity by solving the reliability problem not at the system level, but rather at the level of its 'primitive' constituents: the cells.

Biologically Inspired Hardware Systems

Despite the massive increase in computational power and the great innovation of a new generation of programmable logic devices, faults occurrence in hardware systems leaves engineers with an immense challenge. Traditional fault tolerant methods have proven to be unreliable and costly. This led to consider other alternatives in order to ensure reliability. The alternative was inspired by nature and specifically from the multi-cellular living organisms that exhibit a range of desirable characteristics such as: evolution, adaptation, and fault tolerance. However, in order to build such a biologically inspired hardware system, which attains a desired behaviour, it is necessary to understand the fundamentals of natural organization since the very beginning of life. This led Sanchez et al to introduce the POE (Phylogeny, Ontogeny and Epigenesis) classification. This ►



Top
Figure 2: The POE space model. (Sipper et. al., 2005)

Above:
Figure 3: Four possible combinations in POE Model

method illustrates the three methods of progression in the development of life on earth (Hardman, 2003; Sipper et. al., 2005).

The field of bio-inspired multi-cellular implementation of electronic systems (Embryonics) falls under the ontogeny space in the POE model, which was introduced in a paper by Sipper and collaborators (Sipper et. al., 2005 and references within). This is the three dimensions space in which the bio-inspired systems are plotted (Figure 2). Ontogeny studies the growth and development of organisms from the fertilized egg to its multi-cellular form. It involves cellular division and differentiation of the mother cell and production of daughter cells. Each daughter cell process a copy of the original genome -genome corresponds to the function unit in an electronic cell- and it is composed of genes which are the functions that can be executed.

Embryonics

The inspiration comes from the biological embryonic process that demonstrates the development of a multi-cellular organism

from one fertilized cell, hence Embryonics should import features of the cellular organization and implement a new family of Field Programmable Gate Array (FPGA) in order to show the emergent properties of self-repair, self-reproduction and parallelism. FPGA is a type of logic chip that can be programmed and is organised in arrays of digital cells. They are especially popular for prototyping integrated circuit designs which support thousands of gates. The principle of Embryonics then is to use cell based architecture (artificial electronic cell) to build larger organisms in a similar manner to the embryological development of biological cells. In order to achieve this, the fundamental characteristics of multi-cellular living beings must be applied; this includes Multi-cellular organization, Cellular division, Cellular differentiation (Prodan, L et al 2000) (Zhang, Dragffy et. al., 2003). From the embryonics perspective this can be achieved as follows (Mange et. al., 2000):

Multi-cellular organization: the artificial organism (ORG) is broken down to a finite set of artificial cells (CELL). Each cell being functionally distinctive (Mange, D et al 2000) with the artificial DNA or genome divided into three categories, the ribosomal genome (RG), polymerase genome (PG) and the operative genome (OG). The latter contains all possible genes that can be expressed (executed) by cells in the artificial organism.

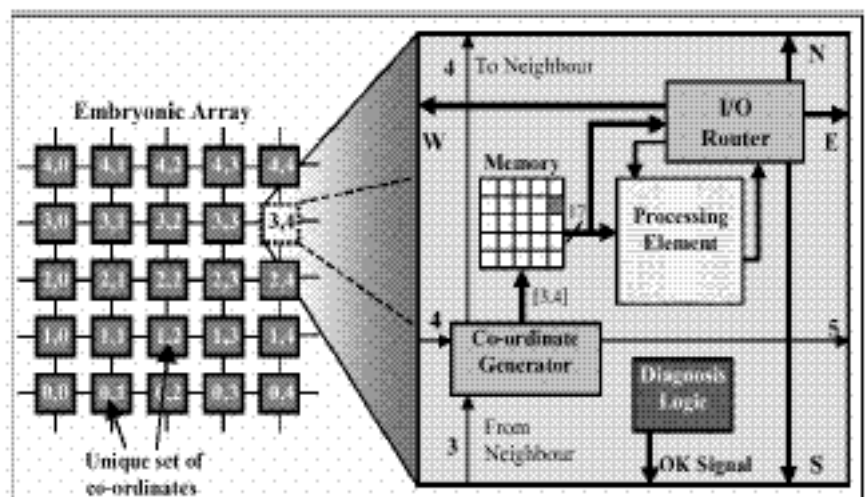
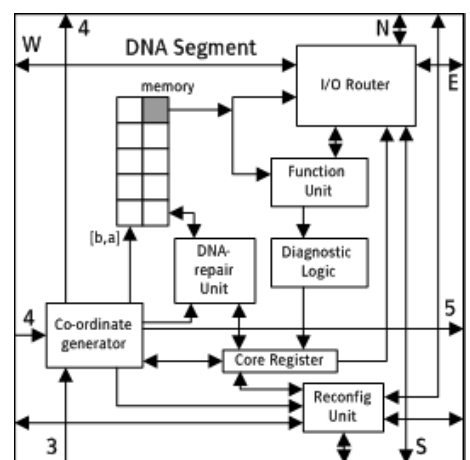
Right:
Figure 4: UWE model of an Embryonics system (one cell). (Zhang, Dragffy et. al., 2003)

Below:
Figure 5: University of York Embryonics model. (Zhang, Dragffy et. al., 2003)

Cellular division: this is concerned with copying the operative genome (OG) from the mother cell to daughter cells. In artificial life, initially the mother cell harboring a copy of the operative genome is defined with its primary coordinates, and then during the process of division, the chip is programmed so that the mother cell will transmit the DNA (genome) to the neighboring cells creating two daughters. The process of division continues in a loop system until all cells in the array have been completely programmed (Zhang, Dragffy et. al., 2003).

Cellular differentiation: this process characterizes each cell within the organism with a particular function. It defines the exact genes in the genome that can be interpreted and executed by each cell depending essentially on its physical position in the array.

All research groups who contribute to the Embryonics project have started from the molecular cell biology; as a consequence similar architectures are expected to be developed. Because of the limitations of the current technology, unlike their liv- ▶



Right:

Figure 6: row elimination reconfiguration technique in an embryonics system (Zhang, Dragffy et. al., 2003).

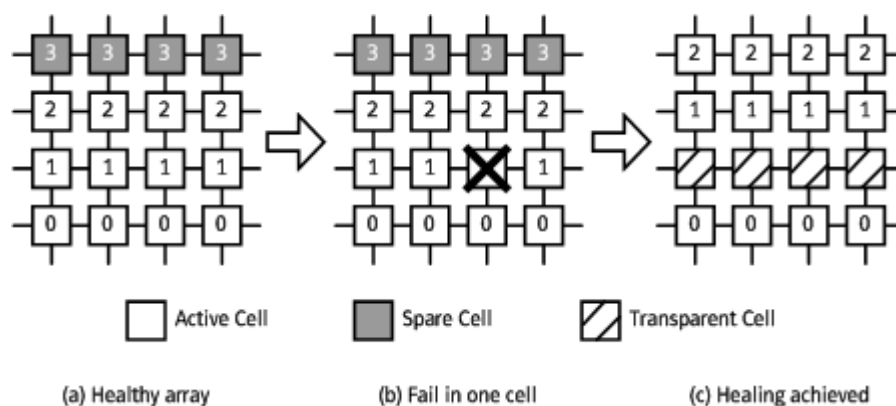
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Figure 7: cell elimination technique for fault tolerance in an embryonics system (Zhang, Dragffy et. al., 2003).

ing counterparts, cells on silicon cannot grow, therefore, all systems embrace cell redundancy as an alternative. So when any cell in the array gets infected (faulty), it is removed and replaced with a healthy one (Prodan et. al., 2000; Zhang, Dragffy et. al., 2003).

Researchers at the University of the West of England (UWE) are taking part in the Embryonics project by proposing an alternative architecture of the Embryonics system, which is a modified version of the University of York's two layers model (Zhang, 2003; Zhang, Dragffy et. al., 2004) (Zhang, X et al 2004). The system is a multi-cellular embryonic array that is capable of self-diagnosis, self-repair and fault recovery. Figure 4 illustrates the architecture of a cell in an array. It contains eight main elements: DNA segment memory, DNA-repair unit, function unit, diagnostic logic, I/O router, co-ordinate generator, reconfiguration unit and a core register (Zhang, Dragffy et. al., 2003).

Reconfiguration mechanism is established when a fault in the array is detected, the system recovers and continues working properly. Two techniques have been defined thus far: row elimination and cell elimination. In row elimination, when one cell is infected it causes the whole row to be transparent or eliminated. Then, the original row shifts to the north finding a spare row to be substituted (Figure 6). This proved to be inefficient as one cell failure causes the array to waste a whole one row. Therefore, an alternative reconfiguration technique became more desirable. The new approach is to apply cell elimination strategy. When a cell is faulty, it is replaced by a spare cell in the same row. This process continues until sufficient



number of spare cells is removed, and subsequently, the row elimination process can be applied (Figure 7). This process causes an increase in complexity of the embryonics system (Zhang, Dragffy et. al., 2003).

Conclusion

Researchers' attempts in the areas of Embryonics and Immunotronics have been successful in many fronts. They have proved the feasibility of the project and made significant progresses in relatively short time scale. However, the ultimate aim of having a reliable hardware system, which fulfils the POE spaces, with self-diagnostic, self-repair, self-reproduction and fault tolerance abilities similar to their counterparts in living beings is far from being done. Both the Embryonics and the Immunotronics are still in their infancy; therefore significant enhancements are required especially when a new field Immuno-Embryonics is born. ■

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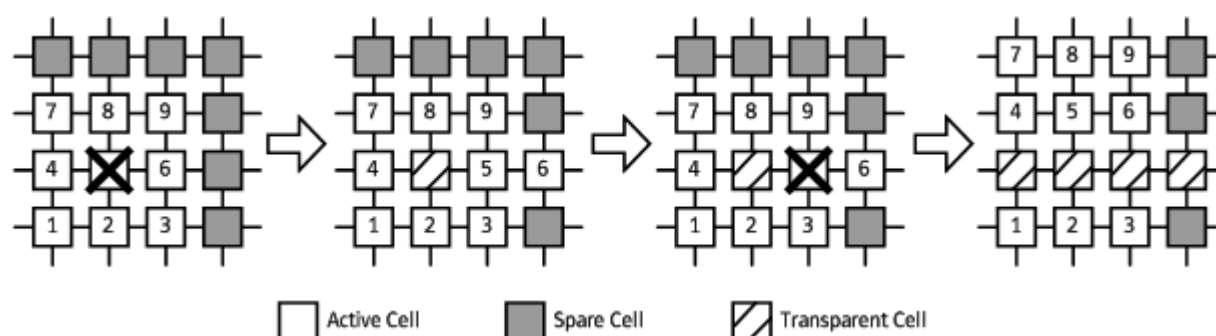
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A Brief History of the Open Source Paradigm

Open source software is primarily rooted in the hacker culture. In 1984, an MIT programmer named Richard Stallman started a project called GNU (recursively standing for "GNU Not Unix") to build a free operating system similar to UNIX. Stallman developed various tools including a text editor and a C compiler that would eventually be used to develop the envisioned operating system. Later on, Stallman founded the Free Software Foundation (FSF) as an umbrella for all GNU development activities and to promote the free software ideology. Free software in the FSF's terminology meant access to the source, not economically free. Stallman explains this as "Free software is a matter of liberty, not price. To understand the concept, you should think of 'free' as in 'free speech,' not as in 'free beer.'" While the GNU project has yet to deliver an operating system, it has produced a good collection of tools that became the basis to many parts of the Linux operating system.

Through the FSF, Stallman introduced a legal form to protect and encourage the ideology of free software. This was crystallized in the release of the "Copyleft" license, a counter license to the conventional copyright restrictions. The aim of Copyleft was to protect the user rather than the developer. The legally binding license allows users to redistribute and change the software, as well as restrict anybody from closing the source code that was initially copylefted, hence enforcing its ideology. After that, The FSF introduced the General Public License (GPL), which is the most popular license nowadays (SourceForge.net). The GPL states that software can be created, changed, copied and distributed under its terms as long as the same rights are passed to the acquirer of the software.

In the mean time, another hacker called Linus Torvalds, using the code base of Minix, an operating system developed by Andy Tanenbaum for teaching purposes, started working on Linux. Linus released a working kernel under the original name, Minix, in an Internet newsgroup as a toy with no intention to compete with the GNU. Accidentally, the small toy gained popularity and momentum. It was renamed Linux, after Linus, and received significant contributions from users. This

OPEN SOURCE SOFTWARE

A Paradigm Shift

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success is attributed to Torvalds leadership, who was very focused on developing the software as opposed to Stallman who was very consumed by the philosophical and ideological issues. Over the years, Linux gained more popularity and respect within commercial environments.

In 1997, Eric S Raymond wrote "The Cathedral and Bazaar", an essay on open source development methods practiced. Raymond distinguished two styles of development; a cathedral and a bazaar. In Raymond's so-called cathedral, a leader sets the goals, coerces programmers to participate, uses extrinsic rewards (e.g. money, promotions), and controls the product and its secrets. In the bazaar, a leader shares a vision, invites programmers, rewards their contributions with fame and gratitude, and shares the product as open source. Raymond emphasizes the fame reward, using the theory of gift/rep-utation culture to explain programmers' eagerness to work hard on code and then give it away.

Under the pressure of fierce competition from Microsoft, Netscape was facing increasing loss of web browser market share. Netscape got interested in the ideas popularized by Raymond and recruited him to lead its strategy to open the source code of Netscape Navigator under the name Mozilla. While the move, executed in 1998, did not really affect Netscape's market share, it brought the open source ideology to the masses. Netscape had a high profile back then after its initial public offering in 1995, which is considered the start of the Internet/dotcom boom.

After the Mozilla release, Raymond organised a meeting with various players

in the open source arena. This convention concluded with setting up the Open Source Initiative (OSI). The OSI was introduced as a more tolerant and commercially friendly alternative to the FSF. The OSI used a totally different language to that of the FSF and courted big IT corporations as well as the media. The aim was to publicise open source as a valid development methodology as opposed to an underground radical movement. The OSI has been very successful in achieving its goals. The OSI has also put a lot of effort into establishing a certification mark to qualify licenses that conform to the Open Source Definition.

Since 1998, open source has taken off in a very noticeable way. Linux rose to the third place among operating systems, the LAMP package has been adopted by many web based organisation as well as web hosting companies, and many software houses have released source code to the community. A quick browse through SourceForge.net, the most popular open source development portal, demonstrates the variety and quantity of software being developed under the terms of the new paradigm.

Definition of Open Source

When open source was originated as free software, Stallman referred to free software as one that gives the user the freedom to:

1. Run the program, for any purpose.
2. Study how the programs work, and adapt it to their needs.
3. Redistribute copies so they can help their neighbour.
4. Improve the program, and release their improvements to the public, so that the whole community benefits.

With the formation of OSI, Raymond and his associates set as one of their main aims the clarifying that that is more to open source than access to the source code. The OSI released the Open Source Definition (OSD), which encompasses thinking from various parties involved in the movement. The OSD states that the distribution terms of open source software must comply with the following criteria:

1. The ability to distribute the software freely.
2. The availability of the source code. ►

3. The right to create derived works through modification.
4. The integrity of the author's source code must be preserved, making the source of changes clear to the community.
5. No discrimination against persons or groups both for providing contributions and for using the software.
6. No restriction on the purpose of usage of the software, providing no discrimination against fields of endeavour.
7. The rights attached to the software apply to all recipients of its (re)distribution.
8. The license must not be specific to a product, but apply to all sub-parts within the licensed product.
9. The license must not contaminate other software, permitting the distribution of other non-open source software along with open source one.

It is clear from the above definitions that the insiders' view is more concerned with the rules distinguishing software distributed as open source from software distributed in a proprietary form. The OSI uses the OSD to certify open source licenses such as the GPL. These definitions do not clarify how open source in general differs from closed source software, i.e. what characteristics are specific to OSS. These characteristics can be summarised in 7 points:

1. They conform to the OSD.
2. They are essentially community efforts.
3. They have a defined process for accepting contributions.
4. Contributors are intrinsically motivated by personal interest, as well extrinsically through peer recognition.
5. Developers are always users.
6. Development is both evolutionary and revolutionary.
7. The code is extremely modularised.

Some of these characteristics, especially number 3, vary in practice from project to another.

The Open Source Development Methodology

The open source paradigm not only introduces a new way for distributing software

but also a whole new method for developing programmes. Eric Raymond dubs the OSS development communities a "bazaar", referring to a loosely coupled, unstructured and varied group but still working on a common goal. Raymond contrasts this to the old fashioned closed software houses, which he names "cathedrals", where the teams are structured and projects tightly managed. While the OSS processes are in debt to traditional software developing concepts, they have adapted these to suit the hacker culture that started OSS. Raymond compares the OSS movement to academia; he states that open source developers welcome peer review as much as academics do; a trait that can not be possible if the source was closed. In his essay, Raymond identified the following principles that underpin the OSS development process:

1. Every good work of software starts by scratching a developer's personal itch.
2. Good programmers know what to write. Great ones know what to rewrite (and reuse).
3. "Plan to throw one away; you will, anyhow." (Fred Brooks, *The Mythical Man-Month*, Chapter 11).
4. If you have the right attitude, interesting problems will find you.
5. When you lose interest in a program, your last duty to it is to hand it off to a competent successor.
6. Treating your users as co-developers is your least-hassle route to rapid code improvement and effective debugging.
7. Release early. Release often. And listen to your customers.
8. Given a large enough beta-tester and co-developer base, almost every problem will be characterised quickly and the fix obvious to someone. Or, less formally, "Given enough eyeballs, all bugs are shallow."
9. Smart data structures and dumb code works a lot better than the other way around.
10. If you treat your beta-testers as if they're your most valuable resource, they will respond by becoming your most valuable resource.
11. The next best thing to having good ideas is recognising good ideas from your users. Sometimes the latter is better.
12. Often, the most striking and innovative solutions come from realising that your

concept of the problem was wrong.

13. Perfection (in design) is achieved not when there is nothing more to add, but rather when there is nothing more to take away.
14. Any tool should be useful in the expected way, but a truly great tool lends itself to uses you never expected.
15. When writing gateway software of any kind, take pains to disturb the data stream as little as possible-and never throw away information unless the recipient forces you to!
16. When your language is nowhere near Turing-complete, syntactic sugar can be your friend.
17. A security system is only as secure as its secret. Beware of pseudo-secrets.
18. To solve an interesting problem, start by finding a problem that is interesting to you.
19. Provided the development co-ordinator has a communications medium at least as good as the Internet, and knows how to lead without coercion, many heads are inevitably better than one.

Raymond also observes that OSS project do not tend to have deadlines for delivery, and that the projects that really take off are the ones where an initial working prototype was made available by the project founder.

Some of the attributes observed are similar to structured methodologies, while others contradict conventional wisdom and give OSS development its individuality. This uniqueness is conceived in the life-cycle of OSS projects.

Usually an OSS project starts as individual's personal interest like what happened with Linus and Linux. The developer then releases initial code that can be built and run. This point is considered a necessity for the project to receive interest from potential contributors. The project is normally split into smaller modules and responsibility over them is passed to module owners. Module owners oversee the development of the specific module and co-ordinate the contributions received.

Contributors download the source code and review it. Any contributions are sent via e-mail or using a Concurrent Versions System (CVS). The donated code is forwarded to all interested parties who have signed up on the mailing list, or accessed directly through the CVS. A vote is ►

then held to decide which contributions are to be accepted. The module owner then commits the changes to the original code. Nightly builds are made from the CVS and users can download the latest versions at all times.

The Internet plays a major role to the development of open source. The projects are normally held on web sites where they are accessible to the public. Nowadays, most projects are hosted by online OSS labs such as SourceForge.net; SourceForge is the most popular with over a 100,000 projects and over a 1,000,000 users.

The online development labs are used for communication within the development community and with end users. Developers share ideas and project responsibilities via online discussion boards and task lists. E-mail and email-lists are highly used within the communities for both discussions and code contributions. Users can feed back to the developers through feature requests and bug reporting. OSS projects have their bug databases published interactively on the web to enable

users to add and search bugs, and to allow developers to find the issues that need fixing.

The striking visible difference between open and closed source is that open source does not see any distinction between the developers and the end users. Opening the source code revolutionises the relation between the coder and the user. One might still question whether this infrastructure is used effectively, and whether the end user is engaged in reality. One of the aims of this project is assessing the contribution of end users to the bug reports and to reliability.

A Final Word

Thanks to the efforts of the many developers contributing to Open Source software, many users can enjoy software that is free and modifiable. Besides the great product the OSS movement has delivered (Apache, PHP, FireFox and many others), it has introduced fresh thinking to the software

developed. The ideology is now spreading to Biotech (bioforge.org), content (wikipedia.org), education (ocw.mit.edu) and fun (opencola.org). ■

Further Reading

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The Next Generation SoC Interconnect Fabric

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Most of the System-on-Chip (SoC) designs, nowadays, are using synchronous interconnect solutions, where a global clock spans the whole system. As the SOC designs are getting more complex, clock skew and propagation delays problems are being introduced (B. Ackland et al, 2000).

Network on-chip is an alternative interconnect solution, where the SOC is regarded as a network of components and packets are routed instead of wires. Network on-chip architectures may provide the right solution to the synchronous approach timing problem and ensures the progress of Moore's law.

By 2007 System-on-Chip (SoC) designs will be using 65nm technology and will grow to two billion transistors (EES, 2003). This will impose critical design challenges that

As the complexity of SoCs rise, the synchronous approach faces problems like increasing signal propagation delays and clock skew problems

should be addressed in the near future. The main challenge that faces designers of SoC integrated circuits is achieving the required functionality, performance and testability whilst minimising design cost and time to market (Benini et al, 2002). The key for achieving this is a methodology that moves design from the circuit level to system level, concentrating on the selection of appropriate pre-designed Intellectual Property (IP) blocks and their interconnection into a complete system.

The interconnection fabric is a key component in any SoC design; it is considered as the limiting factor for achieving SoC's operational goals. Up until now, the indus-

try has only adopted synchronous parallel buses such as ARM's AMBA and IBM's CoreConnect (Collins 2004). They rely on using a global clock to control the transfers. As the complexity of SoCs rise, the synchronous approach faces problems like increasing signal propagation delays and clock skew problems. Other challenges might arise as

well, such as increased power consumption and electromagnetic emissions. As a result, the synchronous approach becomes inefficient and new techniques need to be adopted.

One approach might be to move to asynchronous logic, in which the flow of operand data, rather than a master synchronous clock, controls the flow of results. The APT research group at Manchester University has presented an asynchronous interconnect solution. It promises low power consumption and low electromagnetic emissions. But the difficulty of designing asynchronous systems has limited the technique's use to applica-

tions such as smartcards and pager IC designs.

Another approach would be the use of on-chip micro networks. The approach views the SoC as a network of components. In other words, it regards the SoC as a distributed system on a single silicon substrate. A lot of universities around the world are carrying out research in this area like Stanford in the USA, Manchester in the UK and Pierre and Marie Curie University in France. Many research projects have been started and most are still in the proposal stage with limited published quantitative data as evidence of appropriateness of the adopted approach. In the

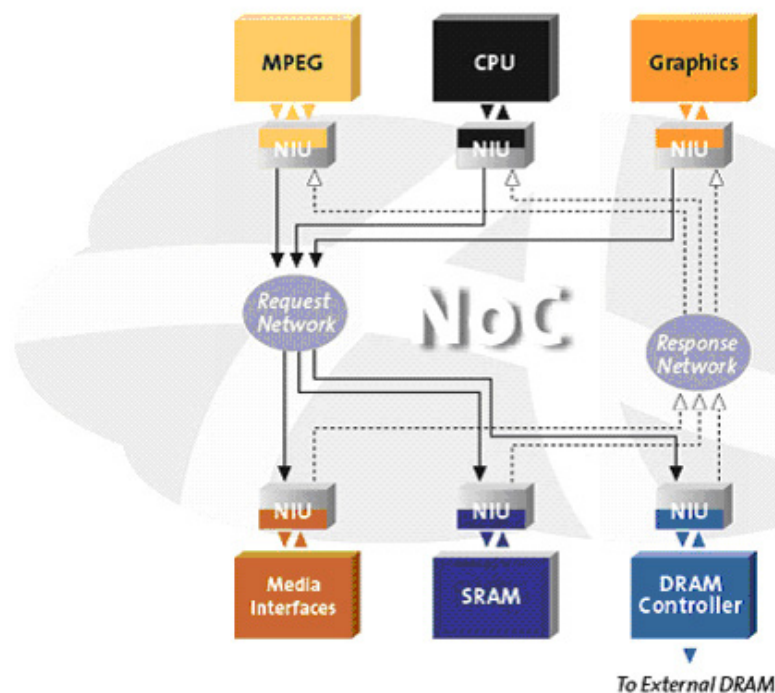
The GALS approach enables the network on-chip to interconnect many IP Blocks with completely independent clock domains.

other hand, there are a few start-up companies who are claiming that they can provide networks on chip solutions. The most interesting ones are:

- Arteris, a 2003 start-up in Paris
- Silistix: a late 2003 start-up from the Amulet group in Manchester University.

The network on-chip NoC must have low communication latency, low communication energy consumption and provide reliable interconnection of components in a plug-and-play fashion. Different methods or techniques are being implemented to achieve the required functionality. Most chip designers see the need for GALS, which stands for Globally Asynchronous Locally Synchronous. As the name states the different IP blocks are connected asynchronously. This reduces the problems of clock skew and increased signal propagation delay. The GALS approach, also, assumes that the IP blocks are synchronous giving it the advantage of being able to reuse the available synchronous IP libraries. In other words, the GALS approach enables the network on-chip to interconnect many IP Blocks with completely independent clock domains.

Arteris first implementation of NoC uses the GALS approach, where components are implemented in traditional synchronous design style. Special Network Interface Units (NIUs) are needed to connect the different IP blocks to the network. These interface units can also bridge ►



Above:
Figure 1: A typical SoC that uses Arteris NoC technology (Arteris, 2000)

between the network and traditional bus protocols such as AMBA in order to achieve backward compatibility.

We believe that future chips are going to look and work like computer networks. Evaluation tools and methodologies used in computer network design will become relevant for SoC design and evaluation. Therefore, models, techniques and tools from the network design field should be used and applied to the SoC design.

However, the challenge is that SoC networks differ from computer networks in their local proximity. SoC networks also exhibit less non-determinism and have some unique characteristics such as energy and power constraints. Therefore we need to adapt the conventional network design and verification methodologies appropriately for network on chip methodology.

Conclusion

Network on-chip technology is getting interest rapidly, but it is still not at all level to be adopted by the industry. Traditional buses architectures, however, are the most widely used interconnect solution. Part of such parity is interconnection implemen-

tations.

SoC designers need to embrace different ways of interconnecting cores together to overcome the problems introduced by traditional synchronous buses. This is most likely to be Networks on-chip. Doctor Giovanni from Stanford University claims that: "On-chip networks will meet the distinctive challenges of providing functionally correct and reliable operation of interacting SOC components"

Glossary

System On-Chip (SoC). A SoC is a representation of interconnecting different components of a computer system on a single chip, in order to achieve certain functionality. These components are called IP blocks; they might be processors, memory controllers, graphics modules ...etc

A typical SoC consists of a number of masters that initiate different operations and a number of slaves that respond accordingly to achieve the required task. An example of a SOC might be a mobile phone controller, where the processor is the master and other modules such as memory and LCD, are slaves.

Clock Skew. In complex synchronous digital systems, a global clock is often distributed across all system parts. These differ-

ent paths introduce different propagation delays, which in turns lead to unacceptable degradations in overall system-timing margins. In other words, the clock signal arrives at different components at different times. This phenomenon is referred to as clock skew. It is mainly due to two causes. The first is the material flow and the second is the distance that the signal has to travel. ■

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It's Time for Us to Give Something Back!

Since the independence in 1962, the Algerian government has invested heavily in higher education for students abroad, especially those with potential. This investment has costed the Algerian government huge sums of money over the years. The purpose of this investment was that the students who study abroad would eventually go back to Algeria and share the good of what they have learned with others. Hence, the gap between Algeria and the West, particularly in science, would be narrowed. However, things did not go according to the plan as only very few people did go back. This resulted in the West developing in mega-fast speed in the science field, while we, in Algeria, have made only small improvements, if not at all.

For us, Algerian students who are blessed to be studying abroad, we have a huge responsibility upon our shoulders. This responsibility is to appreciate what we have learned during our studies abroad and then share it with our fellow countrymen. The way by which we can share our knowledge with the rest could be done in numerous ways, which are all simple and easy if you care and have the will. These include releasing your knowledge on inter-

net sites, which are easily accessible to Algerians, and publishing on magazines, newspapers, journals, etc. In addition, knowledge could be shared by giving talks and lectures during conferences and meetings. However, if we fail to let others benefit from what we have learned, we will not achieve what we have been sent to do. In fact, that will be “the great betrayal” to our country, our families, everyone who trusted us and most importantly ourselves. Furthermore, our country (Algeria) would remain well behind the West and other developed countries in terms of science and we will delay - if not totally kill- the chance of narrowing the gap between us and them. As a result, the state in Algeria, whether social, economical, political or educational, would stay as it is and never improve or may even get worse.

To be honest, there has never been a better time to share our (scientific) knowledge, as now we have IBScientific, where we could publish and share what we know. In other words, the ball now is in our field (Algerian students and researchers) to deliver the goods and if we fail, we will have only ourselves to blame. So, let's get writing, publishing and sharing our knowledge which, as a result, would benefit and educate others. ■

Youcef Mehellou
Cardiff University

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